1 377 573

PATENT SPECIFICATION

(11) 1 377 573

(21) Application No. 15715/72 (22) Filed 5 April 1972

(31) Convention Application No. 21288/71 (32) Filed 5 April 1971

(31) Convention Application No. 25170/71 (32) Filed 19 April 1971

(31) Convention Application No. 25526/71 (32) Filed 20 April 1971

(31) Convention Application No. 60242/71 (32) Filed 11 Aug. 1971 in

(33) Japan (JA)

(44) Complete Specification published 18 Dec. 1974

(51) International Classification C07D 99/22, 99/24

(52) Index at acceptance

C2C 1313 1314 200 214 215 220 221 225 226 22Y 246 247 254 256 25Y 28X 29X 29Y 305 30Y 313 31Y 321 328 32Y 339 342 34Y 351 352 357 364 366 368 36Y 440 638 648 650 652 662 670 682 699 720 748 790 79Y KE LZ MG

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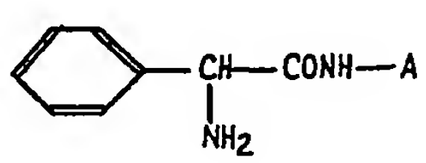
(54) NOVEL ACYLOXYALKYL ESTER DERIVATIVES OF PENICILLIN AND CEPHALOSPORIN

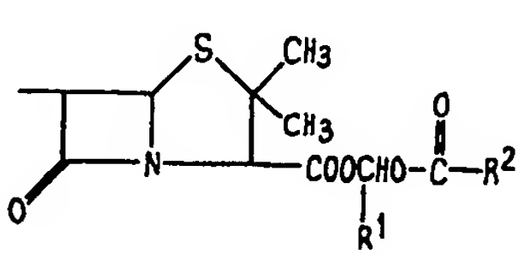
(71) We, YAMANOUCHI PHARMACEUTICAL CO. LTD., a Japanese Company of No. 5—1, Nihonbash-Honcho 2-chome, Chuo-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to acyloxyalkyl ester derivatives of penicillin and cephalosporin each capable of being readily absorbed by the intestines when it is orally administered and showing antibacterial activity by splitting its ester bond in the body. More particularly, the invention relates to an acyloxyalkyl ester derivative of 6-(α-aminophenylacetamido)penicillanic acid, 7-(α-aminophenylacetamido)cephalosporanic acid, or 7-(α-aminophenylacetamido)desacetoxycephalosporanic acid represented by the general formula

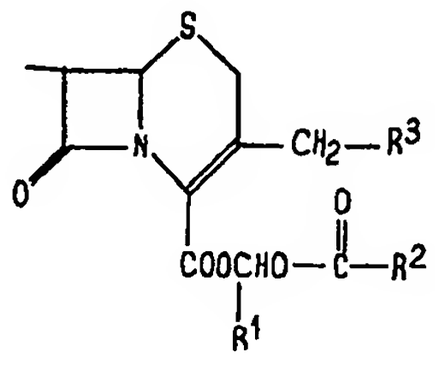


(I)

wherein A represents



or



wherein R^1 and R^2 each represents an unsubstituted alkyl, alkenyl, cycloalkyl, or phenyl group, or a substituted alkyl, cycloalkyl, alkenyl, or phenyl group wherein the substituent is a phenyl group, a phenoxyl group, or a halogen atom or atoms and R^3 is a hydrogen atom or an acetoxy group; and mineral acid-addition salts of the compounds.

Although 6-(α-aminophenylacetamido)penicillanic acid (hereinafter, this acid is simply called " ampicillin ") is well known as a semi-synthetic penicillin that can be orally administered, the extent of the absorption on oral administration is not necessarily sufficient and thus it has generally been desired to increase the amount of ampicillin absorbed on oral administration. As ampicillin derivatives showing remarkably increased absorption on oral administration, the acyloxymethyl esters of ampicillin have been developed. In particular, the pivaloyloxymethyl ester of ampicillin (generally called " Pivampicillin ") has been developed (Belgian Patent No. 721,525 and Jour. Med. Chem., *13*, 607—612 (1970)).

Also, for the same reason, the acyloxymethyl esters of each of 7-(α-aminophenylacetamido)cephalosporanic acid (hereinafter, this acid is simply called " Cephaloglycin ") and 7-α-aminophenylacetamido)desacetoxycephalosporanic acid (hereinafter, this acid is simply called " Cephalexin ") have been developed as readily absorbable derivatives of these acids (German Patent OLS Nos. 1,904,585 and 1,951,012).

It is believed that each of the aforesaid acyloxymethyl esters is absorbed in the intestines and then hydrolyzed enzymatically to formaldehyde and ampicillin. Cephaloglycin or Cephalexin, as the case may be. Thus, the problem of increasing the absorption on oral administration of ampicillin, Cephaloglycin and Cephalexin has been solved by the development of their acyloxymethyl esters. However, these acyloxymethyl esters have not yet been used practically as medicaments since hepatotoxicity has unfortunately been found during their toxicological evaluation (Antimicrobial Agents and Chemotherapy—1970, pages 442—454, in particular, page 453).

It has hitherto been known that formaldehyde is very toxic, about 50 times as toxic as other aldehydes having molecular weights larger than that of formaldehyde (Chemical Abstracts, *45*, 4824h (195 and ibid., *55*, 8653d (1961)), and is especially bad for the liver (Biochem. Pharmacol., *16*, 1533—1537 (1967); Chemical Abstracts, *69*, 58092x (1968); and Biochem. Jour., *111*, 665—678 (1969)). Upon considering these known facts, the inventors have considered that the above-mentioned heptatotoxicity of the acyloxymethyl esters is due to the formaldehyde produced from the ester in the body by the hydrolysis thereof and have therefore intended to produce acyloxyalkyl esters other than the acyloxymethyl esters (hereinafter the term " acyloxylalkyl ester or esters " excludes the acyloxymethyl ester or esters) of ampicillin, Cephaloglycin, and Cephalexin as their readily absorbable derivatives which do not produce formaldehyde in the body.

Although as mentioned above, the pivaloyloxymethyl ester of ampicillin is known, the acyloxyalkyl esters intended by the inventors have not yet been reported in any technical literature and also processes of producing these esters have not yet been known. Furthermore, the productions of these esters was considered to be difficult. This is because although there is a description about the starting materials of the compounds of this invention, such as the acyloxyalkyl esters of benzylpenicillin in " Journal of Chemical Society ", 2127—2130 (1965), in particular pages 2128—2129, it is described in the same report that the acyloxyalkyl esters of benzylpenicillin (except the acyloxymethyl ester thereof) were generally reluctant to crystallize (and hence troublesome to obtain pure) and there are no practical descriptions about the productions of these esters.

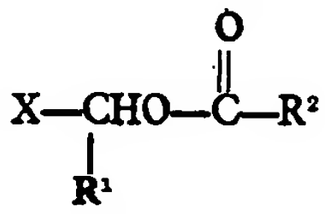
By the reaction of the potassium salt of a natural penicillin, i.e. benzylpenicillin with a 1-acyloxyalkyl halide we have succeeded in obtaining the acyloxyalkyl ester of benzylpenicillin in a comparatively pure state. Furthermore, we have also obtained the acyloxyalkyl esters of natural cephalosporin such as an N-protected cephalosporin C by a similar procedure. Thus, it has been found to be possible to obtain the acyloxyalkyl esters of ampicillin or cephaloglycin by treating these compounds in accordance with known methods.

The compounds of this invention are obtained as solids in unexpectedly pure states and as will be described later the results of the animal tests showed that the absorption of these compounds after oral administration was good and the ester bonds were hydrolysed in the blood stream to provide therein ampicillin, cephaloglycin, or cephalexin (as the case may be), which showed antibacterial activity.

It is also one of the merits of this invention that these compounds are stable to β-lactamase. They may be prepared by the following procedures:

(i) Acyloxyalkyl esters of ampicillin or cephaloglycin can be obtained by react-

ing the alkali metal salt of a natural penicillin such as benzylpenicillin or phenoxypenicillin or the alkali metal salt of a natural N-protected cephalosporin such as cephalosporin C with an acyloxyalkyl halide represented by the general formula (IV)



(IV)

wherein R^1 and R^2 each represents an unsubstituted alkyl, cycloalkyl, alkenyl, or phenyl group or a substituted alkyl, cycloalkyl, alkenyl, or phenyl group wherein the substituent is with a phenyl group, a phenoxy group, or a halogen atom or atoms and X represents a halogen atom and then following the method disclosed in the specification of German OLS No. 2,029,195 using the acyloxyalkyl ester compound thus obtained as the starting material, as follows.

The acyloxyalkyl ester of natural penicillin or N-protected cephalosporin C is reacted with a phosphorus halide in an inert solvent in the presence of a tertiary amine. Examples of the inert solvent used in this reaction include toluene, chloroform, dichloromethane, dichloroethane, and trichloroethylene. As the tertiary amine pyridine, N,N-dimethylaniline, or triethylamine may be used, but the use of an aromatic amine such as N,N-dimethylaniline is particularly preferable. As the phosphorus halide, there may be used phosphorus pentachloride or phosphorus pentabromide but the use of phosphorus pentachloride is particularly preferable.

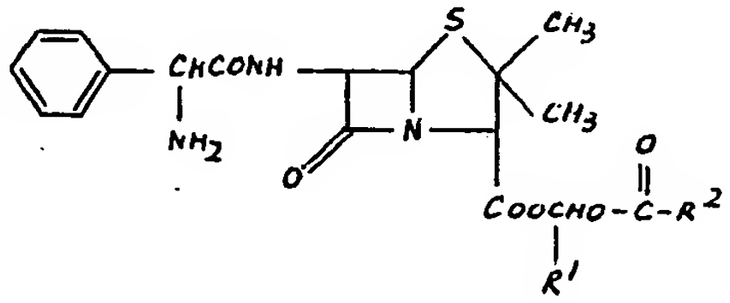
For example, when phosphorus pentachloride is employed, the reaction is conducted under cooling, preferably at a temperature of from 0 to −30°C. The amount of the tertiary amine used in this reaction is preferably 3—5 mols per mol of the phosphorus halide. It is preferable to use an amount of the phosphorus halide slightly in excess of molar with regard to the starting material.

The iminohalide compound thus obtained is caused to react with a lower alcohol without being isolated from the reaction mixture, to form an iminoether compound. As the lower alcohol, there may be used such aliphatic alcohols as methanol, ethanol, or propanol. In this case, it is preferable to use the lower alcohol in molar excess of the imino halide. The reaction is preferably conducted at about the same temperature as that used when preparing the iminohalide as mentioned above.

The iminoether compound is then reacted with phenylglycine or an acylating derivative thereof. Phenylglycylchloride hydrochloride is most preferable among the acylating derivatives of phenylglycin but other acid halides, or acid anhydrides, or mixed acid anhydrides may also be used in this reaction. When phenylglycylchloride hydrochloride is employed, it is preferably added in equimolar proportions in excess thereof to a solution of the iminoether compound with cooling to the same temperature as used in the previous step. Also, it is preferable for the smooth progress of the reaction to include a tertiary amine such as pyridine or N,N-dimethylaniline in the reaction system.

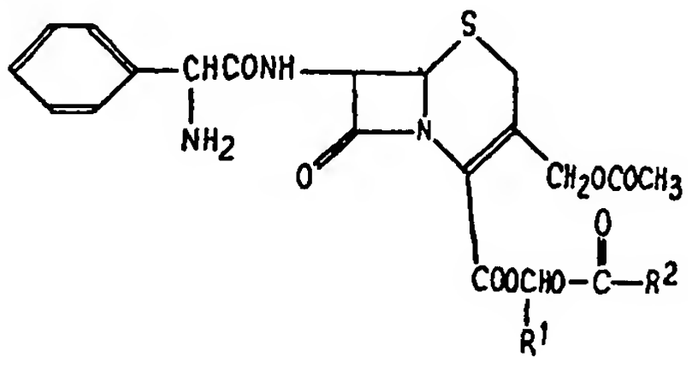
The reaction product thus obtained is finally treated with water or an alcohol. This treatment may be carried out simultaneously with the separation of the desired product.

The acyloxyalkyl ester of ampicillin or cephaloglycin represented by the formula



(II)

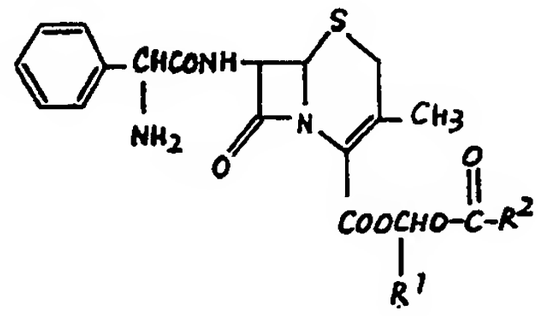
or



(III)

wherein R^1 and R^2 are defined above can be separated by extraction according to a conventional manner.

(ii) The acyloxyalkyl ester of cephalexin may be prepared in the following manner. The acyloxyalkyl ester of a natural penicillin is treated with perbenzoic acid or performic acid to form the corresponding S-oxide compound which is then heated in the presence of an inorganic or organic acid such as phosphoric acid, sulfuric acid, phenyl dihydrogenphosphoric acid, or p-toluenesulfonic acid and a weak base such as pyridine, quinoline or benzimidazole to expand the ring. Then, using the thus formed acyloxyalkyl ester of 7-acylamino-desacetoxycephalosporanic acid as the starting material, the same procedure as in the process (i) mentioned above, (that is, the reactions with a phosphorus halide, a lower alcohol, a phenylglycylchloride hydrochloride, and water or alcohol) is followed to provide the desired product represented by the following general formula

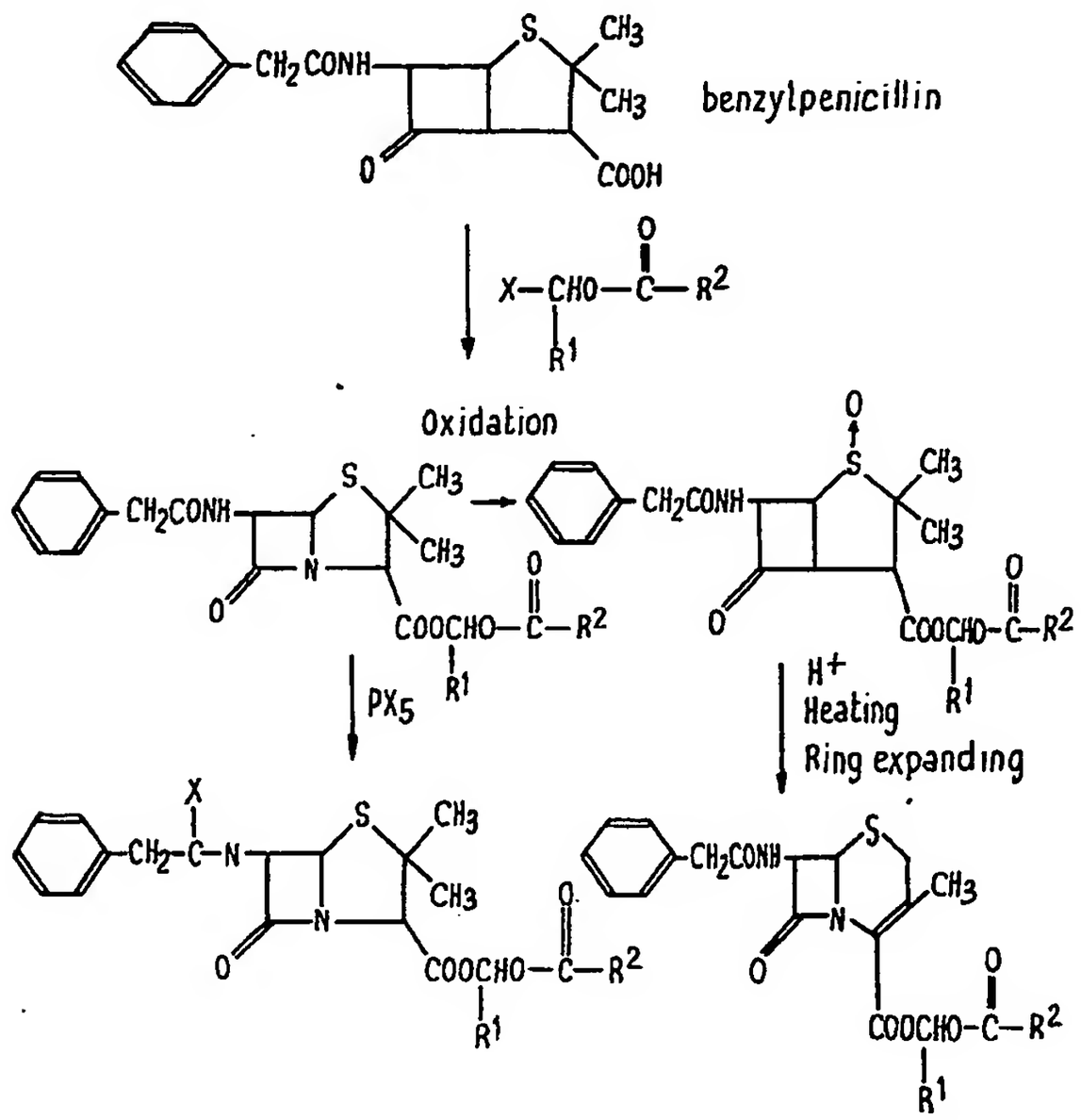


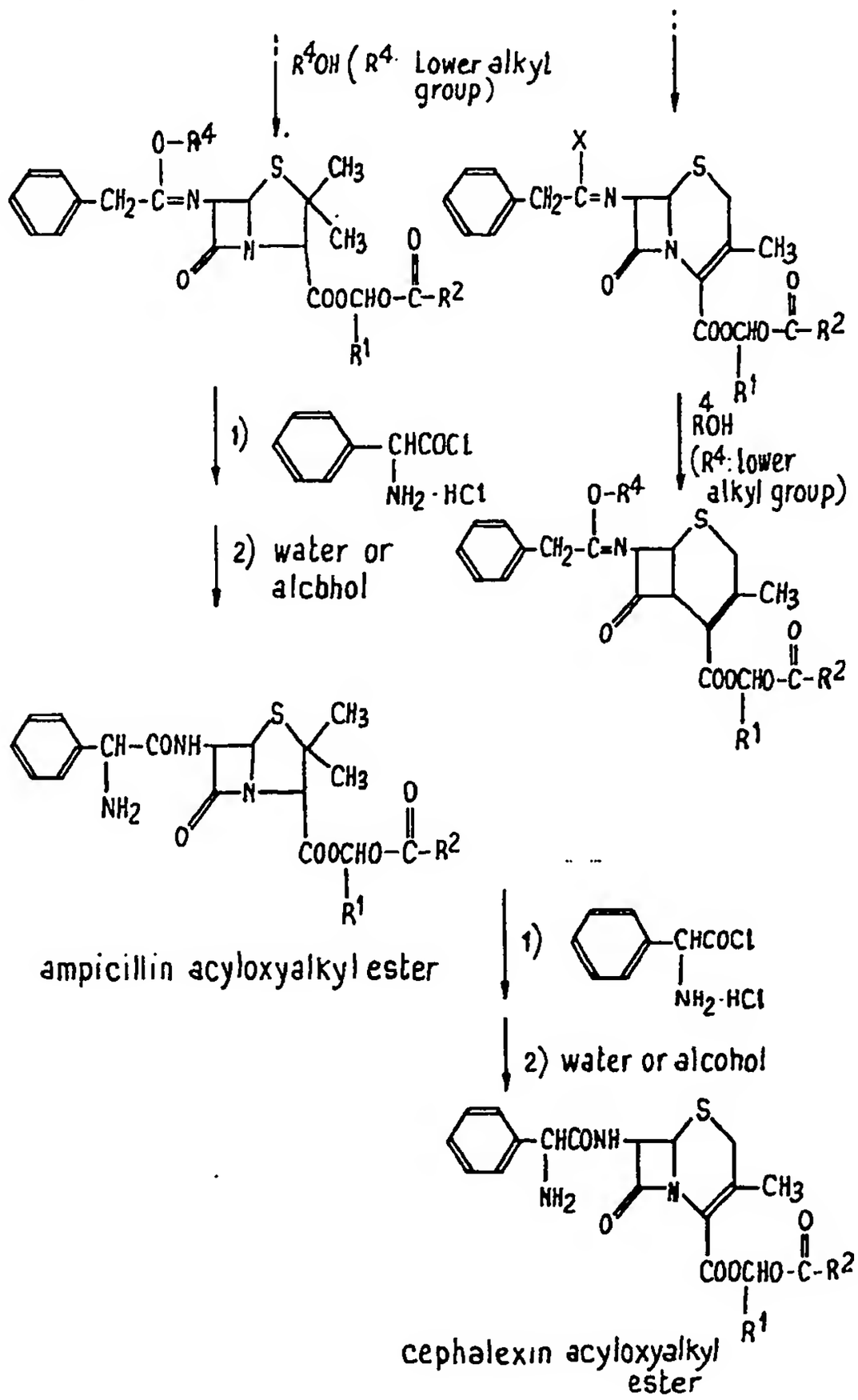
(III')

wherein R^1 and R^2 are as defined above.

(iii) The compounds shown by the above-mentioned general formulae (II), (III), and (III') may also be prepared by reacting each of 6-aminopenicillanic acid, 7-aminocephalosporanic acid, and 7-aminodesacetoxycephalosporanic acid prepared by various known methods with an acyloxyalkyl halide to form an acyloxyalkyl ester and then acylating the acyloxyalkyl ester thus obtained with an acylating derivative of phenylglycine such as phenylglycylchloride, hydrochloride in a conventional manner.

The procedures for preparing the compounds of this invention are illustrated by the following reaction scheme:





Examples of the groups R^1 and R^2 of the compounds of this invention are a straight chain alkyl group such as a methyl group, an ethyl group, a propyl group, a hexyl group or a heptyl group; a branched chain alkyl group such as an isopropyl group, an isobutyl group, a tert-butyl group, or a 2-ethylbutyl group; a cyclic alkyl group such as a cyclopentyl group or a cyclohexyl group; a phenyl group; a phenylalkyl or phenylcycloalkyl group such as a benzyl group, a phenethyl group, a 3-phenylbutyl group, a 2-ethyl-4-phenylbutyl group or a 4-phenylcyclohexyl group; a phenoxyalkyl or phenoxycycloalkyl group such as a phenoxymethyl group, a phenoxypropyl group, or a 3-phenoxycyclopentyl group; a halogen-substituted alkyl or halogen-substituted cycloalkyl group such as trichloromethyl group, a 2-chloroethyl group or a 4-chlorocyclohexyl group; and an alkenyl group such as a vinyl group or an allyl group.

The compounds of this invention are the esters of 6-(α-aminophenylacetamido)-penicillanic acid (generally called ampicillin), 7-(α-aminophenylacetamido)cephalosporanic acid (generally called cephaloglycin), and 7-(α-aminophenylacetamido)desacetoxycephalosporanic acid (generally called cephalexin). The typical examples of these esters are as follows:

	Example No.
1-Acetoxyethyl ester	2.
1-Pivaloyloxyethyl ester	4.
1-Pivaloyloxypropyl ester	—
1-Acetoxy-2-propenyl ester	8.
1-Benzylcarbonyloxybutyl ester	—
1-Cyclohexylcarbonyloxyethyl ester	16.
1-Phenoxyacetoxyethyl ester	20.
1-Acetoxy-3-phenylpropyl-ester	22.
1-Acetoxy-2,2,2-trichloroethyl ester	24.
α-Benzoyloxybenzyl ester	10.
1-Acetoxypropyl ester	6.
1-(2-Ethylbutyryloxy)propyl ester	33.
1-Isobutyryloxy-2-methylpropyl ester	45.
1-Cyclohexylcarbon-1-isobutyloxybutyl ester	41.
α-(3-Phenylpropionyl)benzyl ester	—
1-Benzoyloxy-3-phenylpropyl ester	52.
α-Pivaloyloxybenzyl ester	49.
1-Propionyloxyethyl ester	25.
1-Heptanoyloxyethyl ester	27.
1-Cyclopentancarbonyloxy-2-phenoxyethyl ester	—
1-Octanoyloxyethyl ester	26.
1-(2-Ethylbutyryl)oxyethyl ester	27.
1-(2-Phenylacetoxy)ethyl ester	28.
1-Isobutyryloxypropyl ester	31.
1-(2-Phenoxyacetoxy)-2-methylpropyl ester	42.
1-Acetoxyheptyl ester	47.
1-tert-Butyryloxy-3-phenylpropyl ester	51.
1-(2-Phenylacetoxy)-3-phenylpropyl ester	53.
1-Propionyloxy-2-phenylethyl ester	91.
1-Propionyloxypropyl ester	92.
1-Butyryloxy-1-cyclopentylmethyl ester	94.
1-Butyryloxy-2-ethylbutyl ester	97.
1-Heptanoyloxybutyl ester	96.
1-Butyryloxy-2,2-dimethylpropyl ester	102.
1-Isobutyryloxy-2,2-dimethylpropyl ester	104.
1-(3-Phenylpropionyloxy)propyl ester	—
1-Propionyloxy-2,2,2-trichloroethyl ester	108.
1-(2-Phenoxyacetoxy)butyl ester	109.
1-Cyclopentanecarbonyloxybutyl ester	94.
α-Butyryloxybenzyl ester	110.
1-Benzoyloxypropyl ester	111.
1-Benzoyloxy-2-phenylethyl ester	113.

These ester compounds may be also obtained as the salts of a mineral acid such as hydrochloric acid.

For illustrating the excellent properties of the compounds of this invention, the oral absorbable properties of the compounds of this invention were compared with those of ampicillin and the pivaloyloxymethyl ester of ampicillin, that is, the concentrations of the samples in blood when they were orally administered were measured, the experimental procedure and the results of which are shown below:

Experimental Procedure:

Each of α-aminobenzylpenicillin tri-hydrate, α-aminobenzylpenicillin, pivaloyloxymethyl ester (generally called Pivampicillin) hydrochloride mono-hydrate, and the hydrochlorides of the compounds of this invention shown in the following table was orally administered to rats (male, each group five rats) in an amount equivalent to 20 mg./kg. of α-aminobenzylpenicillin and after 0.5 hours, a blood sample was taken and the concentration of α-aminobenzylpenicillin in the blood plasma was measured in each case. The results are shown in the following table.

Administered material	(A)	Example No.
Ampicillin tri-hydrate	1.	–
Ampicillin pivaloyloxymethyl ester hydrochloride.mono-hydrate	3.80	–
Ampicillin 1-pivaloyloxyethyl ester hydrochloride	5.02	4
Ampicillin 1-acetoxypropyl ester hydrochloride	6.38	6
Ampicillin 1-benzoyloxyethyl ester hydrochloride	4.18	18
Ampicillin 1-propionyloxypropyl ester hydrochloride	4.00	29
Ampicillin 1-propionyloxybutyl ester hydrochloride	5.36	35
Ampicillin 1-pivaloyloxybutyl ester hydrochloride	7.91	39
Ampicillin 1-cyclohexylcarbonyloxybutyl ester hydrochloride	4.24	41
Ampicillin 1-isobutyryloxy-2-methylpropyl ester hydrochloride	4.13	45
Ampicillin α-acetoxybenzyl ester hydrochloride	5.18	48
Ampicillin α-butyryloxybenzyl ester hydrochloride	5.00	14
Ampicillin 1-(2-ethylbutyryloxy)ethyl ester hydrochloride	4.21	27
Ampicillin 1-isobutyryloxybutyl ester	8.29	37

Note: (A) The ratio of the concentration of ampicillin in the blood plasma when each of the above-mentioned compounds was administered to the concentration of ampicillin in the blood plasma when ampicillin tri-hydrate was administered, 0.5 hour after the administration. The first two compounds are known compounds and other compounds in the above table are the compounds of this invention.

In addition, the concentration of ampicillin in the blood plasma 0.5 hour after ampicillin. tri-hydrate was administered was about 1.00 μ g./ml. in each group.

Hydrolysis of cephalexin acyloxyalkyl esters in rat plasma:

Experimental Procedure

Rat plasma solutions each containing cephalexin, or the cephalexin acyloxyalkyl ester of this invention in an amount equivalent to 10 μg./ml. or 2.5 μg./ml. of cephalexin was prepared and after incubating for 30 minutes at 37°C., the plasma solution was superposed on a culture medium containing *Streptococcus hemolyticus* Cook. Then, after pre-diffusion for 2 hours at 4°C., the incubation was carried out for 16 hours at 37°C. and then the length of inhibition zones obtained was measured.

The ratio of antibacterial activity (θ) was measured by the method shown in " Jour. Penicillin ", *1*, 100 (1947), the value of $100\times\theta$ indicates the hydrolyzed percentage.

$$\log\theta = \frac{\log\dfrac{S_H-S_L}{U_H-U_L}}{\log\dfrac{S_L-U_L}{S_H-U_H}} \times \log A$$

in the above formula, S_H and S_L represent the lengths of the zones of inhibition when the solutions each containing 10 μg./ml. and 2.5 μg./ml. of cephalexin respectively are used; U_H and U_L represent the lengths of the zones of inhibition when the solutions each containing 10 μg./ml. and 2.5 μg./ml. of the cephalexin acyloxyalkyl ester of this invention are used; and A is the concentration ratio of cephalexin to cephalexin.acyloxyalkyl ester, that is $10/2.5=4$.

The results are shown in the following table.

Administered material	Hydrolyzed percentage ($100\times\theta$)	Example No.
Cephalexin pivaloyloxymethyl ester hydrochloride (control)	81.6	*
Cephalexin 1-acetoxyethyl ester hydrochloride	74.5	86
Cephalexin 1-propionyloxyethyl ester hydrochloride	82.6	90
Cephalexin 1-propionyloxy-2,2,2-trichloroethyl ester hydrochloride	81.0	–
Cephalexin 1-acetoxypropyl ester hydrochloride	75.7	87
Cephalexin 1-(2-phenylacetoxy)propyl ester-hydrochloride	92.7	91
Cephalexin 1-butyryloxybutyl ester hydrochloride	80.5	98
Cephalexin 1-valeryloxybutyl ester hydrochloride	90.1	101
Cephalexin 1-pivaloyloxybutyl ester hydrochloride	88.2	102
Cephalexin 1-cyclohexylcarbonyloxybutyl ester hydrochloride	89.1	–
Cephalexin 1-benzoyloxybutyl ester hydrochloride	81.0	110
Cephalexin 1-propionyloxy-2-methylpropyl ester hydrochloride	79.5	105
Cephalexin 1-propionyloxyheptyl ester hydrochloride	79.9	–

Administered material	Hydrolyzed percentage	Example No.
Cephalexin 1-acetoxy-3-phenylpropyl ester hydrochloride	84.1	106
Cephalexin 1-propionyloxy-3-phenylpropyl ester hydrochloride	86.2	107
Cephalexin α-(2-phenylacetoxy)benzyl ester hydrochloride	84.9	113

Example 1.

In 100 ml. of acetone was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 1.5 g. of potassium bicarbonate and 10 g. of 1-acetoxyethyl bromide, the resultant mixture was refluxed for 2 hours. The reaction mixture was cooled, filtered, and the filtrate was concentrated under reduced pressure. The residue thus obtained was washed with 30 ml. of petroleum ether, dissolved in 80 ml. of ethyl acetate, and then the solution thus prepared was filtered. The ethyl acetate solution thus prepared was washed with 50 ml. of 5% aqueous sodium bicarbonate solution and then 50 ml. of water, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure. The concentrate was subjected to a silica gel column chromatography and eluted with benzene-ethyl acetate volume ratio, 3:1) solvent and the eluate was concentrated under a reduced pressure to provide 7.5 g. of the colorless powdery crystal of benzylpenicillin.1-acetoxyethyl ester. The yield of the product was 60%.

Example 2.

In 75 ml. of dichloromethane was dissolved 4.2 g. of benzylpenicillin 1-acetoxyethyl ester and after adding to the solution 4.12 g. of N,N-dimethylaniline, the resultant mixture was cooled to −25°C. Then, 2.3 g. of phosphorus pentachloride was added to the solution and the mixture was stirred for 2.5 hours at a temperature of 25°C.±5°C. Then, 45 ml. of methanol was added dropwise to the solution at the same temperature and the mixture was stirred for further 2.5 hours to provide an iminoether solution. To the solution thus prepared was added 6.86 ml. of N,N-dimethylaniline, and then 2.5 g. of D(−)-α-phenylglycylchloride hydrochloride slowly over a one hour period with stirring at a temperature of −25°±5°C. After stirring the reaction mixture for 2 hours at the same temperature, 50 ml. of a cold saturated aqueous sodium chloride solution was added to the reaction mixture and the mixture was stirred for 0.5 hour at a temperature of −5°C. to 0°C. Thereafter, the dichloromethane layer formed was recovered, washed with 30 ml. of 0.5 *N* hydrochloric acid and then 30 ml. of aqueous saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure at a low temperature to provide an oily residue. After adding to the residue 50 ml. of cold water and 20 ml. of ethyl acetate followed by stirring, the aqueous layer formed was recovered. After washing the aqueous layer with 20 ml. of ethyl acetate, 30 ml. of ethyl acetate was added and then 10 g. of sodium chloride was added, followed by stirring. The ethyl acetate layer thus formed was recovered and the aqueous layer was further extracted with 20 ml. of ethyl acetate. The ethyl acetate layer recovered was combined with the ethyl acetate extract obtained in the above procedure, the mixture was washed with 20 ml. of a cold and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at a low temperature. The residue was mixed with 50 ml. of ether and the crystals formed were recovered. The crystals were washed with a small amount of ether and dried to provide 3.5 g. of white powder of ampicillin.1-acetoxyethyl ester hydrochloride having a melting point of 103—105°C. (decomposed) with a yield of 74%.

Elementary analysis as $C_{20}H_{26}N_3O_6SCl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	50.90	5.55	8.90	6.79	7.51
Found:	50.14	5.98	8.35	6.37	7.72

Example 3.

In 120 ml. of acetone was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 5.1 g. of 1-pivaloyloxyethyl chloride and 3 ml. of 25% aqueous sodium iodide solution, the mixture was refluxed for 5 hours. After cooling, the reaction mixture was processed as in Example 1 to provide 8.5 g. of the colorless powdery crystals of benzylpenicillin.1-pivaloyloxyethyl ester with a yield of 63%.

Example 4.

In 75 ml. of dichloromethane was dissolved 4.6 g. of benzylpenicillin.1-pivaloyloxyethyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C. Then, 2.3 g. of phosphorus pentachloride was added to the mixture, the resultant mixture was stirred for 2.5 hours at a temperature of −25±5°C. Then, 45 ml. of methanol was added dropwise to the solution at the same temperature and the mixture was stirred for further 2.5 hours to provide an iminoether solution. After adding to the solution 6.86 ml. of N,N-dimethylaniline, 2.5 g. of D(−)-α-phenylglycylchloride hydrochloride was added slowly to the solution over a one hour period with stirring at −25°±5°C. Thereafter, the mixture was stirred for 2 hours at the same temperature and then processed as in Example 2 to provide 3.4 g. of the white powder of ampicillin.1-pivaloyloxyethyl ester hydrochloride having a melting point of 111—114°C. (decomposed) with a yield of 66%.

Elementary analysis as $C_{23}H_{32}N_3O_6SCl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	53.74	6.27	8.17	6.24	6.90
Found:	53.21	6.86	7.98	5.94	7.03

Example 5.

In 80 ml. of acetone was suspended 7.4 g. of benzylpenicillin potassium salt and after adding to the suspension 4.3 g. of 1-acetoxypropyl bromide and 1 ml. of 25% aqueous sodium iodide solution, the mixture was refluxed for 5 hours. After cooling, to the reaction mixture was added 80 ml. of ice-water and an oily material thus formed was extracted twice each with 100 ml. of ether. The ether extracts were combined. The ether solution thus obtained was washed with 50 ml. of 5% aqueous sodium bicarbonate solution and twice each with 50 ml. of water, dried over anhydrous sodium sulfate, and concentrated under a reduced pressure at a low temperature. The residue was washed with petroleum ether and then an insoluble oily material was recovered by decantation and dried under a reduced pressure to provide 7.0 g. of viscous benzylpenicillin.1-acetoxypropyl ester with a yield of 81%.

Example 6.

In 44 ml. of dichloroethane was dissolved 4.34 g. of benzylpenicillin.1-acetoxypropyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C. Then, after adding 2.3 g. of phosphorus pentachloride, the resultant mixture was stirred for 1.5 hours at −25±5°C. Then, after adding 40 ml. of methanol dropwise at the same temperature, the mixture was stirred for further 2.5 hours to provide an iminoether solution. After adding 6.86 ml. of N,N-dimethylaniline to the solution, 2.5 g. of D(−)-α-phenylglycylchloride.hydrochloride slowly over a one hour period with stirring at −25±5°C. Thereafter, the mixture was stirred for 2 hours at the same temperature and then allowed to stand for 16 hours at a temperature of −20°C. to −25°C. To the reaction product mixture was added 50 ml. of a cold and saturated aqueous sodium chloride solution and the mixture was stirred vigorously for 10 minutes at 0—5°C. Then, the aqueous layer thus formed was separated from the dichloroethane layer formed. The dichloroethane solution thus recovered was washed with 30 ml. of 0.5 *N* hydrochloric acid saturated with sodium chloride and then 30 ml. of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure at a low temperature to provide an oily product.

The oily product thus obtained was dissolved in a mixture of 50 ml. of cold water and 50 ml. of ethyl acetate and then the aqueous layer formed was recovered. The aqueous layer was washed twice each with 20 ml. of ethyl acetate, saturated with sodium chloride, and the oily material thus formed was extracted twice with 30 ml. each of ethyl acetate. The ethyl acetate extracts were combined and the mixture was washed thrice each with 20 ml. of saturated aqueous sodium chloride solution, dried over an-

hydrous magnesium sulfate, and then concentrated under a reduced pressure at a low temperature. When 50 ml. of ether was added to the residue and the mixture was stirred, precipitates were formed, which were recovered by filtration, washed with a small amount of ether, and dried to provide 3.2 g. of the white powder of ampicillin.1-acetoxypropyl ester hydrochloride having a melting point of 95—100°C. (decomposed) with a yield of 66%.

Elementary analysis as $C_{21}H_{28}N_3O_6SCl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	51.90	5.81	8.65	6.60	7.30
Found:	51.03	6.22	8.31	6.05	7.53

Example 7.

In 40 ml. of dimethylformamide was suspended 7.4 g. of benzylpenicillin potassium salt and after adding to the suspension 3.2 g. of 1-acetoxy-2-propenylchloride, the mixture was stirred for 16 hours at room temperature. The reaction mixture dispersed in 50 ml. of ice-cooled water and then extracted twice each with 50 ml. of ethyl acetate. The ethyl acetate extracts were combined. The mixture was washed with 50 ml. of 5% aqueous sodium bicarbonate solution and then 50 ml. of water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure at a low temperature. When the residue was dried under a reduced pressure, 6.5 g. of oily benzylpenicillin.1-acetoxy-2-propenyl ester was obtained with a yield of 76%.

Example 8.

In 43 ml. of dichloroethane was dissolved 4.32 g. of benzylpenicillin.1-acetoxy-2-propenyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C. Then, after adding 2.3 g. of phosphorus pentachloride, the mixture was stirred for 1.5 hours at −25 ±5°C.

Then, 40 ml. of methanol was added dropwise to the solution at the same temperature as above and the mixture was stirred for 2.5 hours to provide an iminoether solution.

The solution was mixed with 6.86 ml. of N,N-dimethylaniline and then 2.5 g. of D(−)-α-phenylglycylchloride hydrochloride was added thereto slowly over a one hour period. Then, after stirring the mixture for 2 hours at the same temperature, the mixture was allowed to stand for 16 hours at a temperature of from −20°C. to −25°C. By processing the mixture as in Example 6, 3.5 g. of the white powder of ampicillin 1-acetoxy-2-propenyl ester hydrochloride having a melting point of 115—118°C. (decomposed) was obtained with a yield of 72%.

Elementary analysis as $C_{21}H_{26}N_3O_6SCl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	52.12	5.41	8.68	6.63	7.33
Found:	51.49	5.90	8.27	6.23	7.60

Example 9.

In 60 ml. of dimethylformamide was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 3.0 g. of potassium bicarbonate and 9 g. of α-benzoyloxybenzyl bromide, the mixture was stirred for 16 hours at room temperature. The reaction mixture was dispersed in 100 ml. of ice-water and extracted thrice each with 50 ml. of ethyl acetate. The ethyl acetate extracts were combined and the mixture was washed with 50 ml. of 5% aqueous sodium bicarbonate solution and then 50 ml. of water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure at a low temperature. The residue was washed with a small amount of petroleum ether and dried under a reduced pressure to provide 12.8 g. of viscose benzylpenicillin α-benzoyloxybenzyl ester with a yield of 78.2%.

Infrared absorption spectra:

νNH 3300 cm.$^{-1}$, νC=O 1790—1760 cm^{-1} (β-lactam, ester), 1740 cm^{-1} (ester), 1660 cm.$^{-1}$ (amide).

Example 10.

In 50 ml. of dichloromethane was dissolved 5.5 g. of benzylpenicillin.α-benzoyloxybenzyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C.

Then, after adding 2.3 g. of phosphorus pentachloride, the mixture was stirred for 1.5 hours at −25±5°C. Thereafter, 40 ml. of methanol was added dropwise to the mixture at the same temperature and the mixture was further stirred for 2 hours to provide an iminoether solution.

To the solution thus prepared was added 6.86 ml. of N,N-dimethylaniline and then to the mixture was added 2.5 g. of D(−)-α-phenylglycylchloride.hydrochloride slowly over a one hour period with stirring at −25±5°C.

Thereafter, the mixture was stirred for 2 hours at the same temperature and 50 ml. of cold and saturated aqueous sodium chloride solution was added to the reaction mixture followed by stirring for 0.5 hour at a temperature of from −5°C. to 0°C. Then, the dichloromethane layer formed was recovered, washed with 30 ml. of 0.5 *N* aqueous hydrochloric acid solution saturated with sodium chloride and then 30 ml. of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated over anhydrous magnesium sulfate to provide an oily residue. The residue was dissolved in a mixture of 100 ml. of cold water, 30 ml. of ethyl acetate, and 20 ml. of petroleum benzine with stirring and then the aqueous layer formed was recovered. The aqueous layer was washed with a mixture of 20 ml. ethyl acetate and 10 ml. of petroleum benzine and then a small amount of activated carbon was added to the aqueous solution followed by filtration. Onto the filtrate was added in layer 30 ml. of ethyl acetate and the mixture was saturated with sodium chloride with stirring.

The ethyl acetate layer formed was recovered and the aqueous layer thus separated was extracted twice each with 20 ml. of ethyl acetate. The ethyl acetate extracts and the ethyl acetate layer recovered above were combined. The mixture was washed with 30 ml. of cold and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at a low temperature. Petroleum ether was added to the residue and the crystal thus formed was recovered by filtration, washed with a small amount of petroleum ether, and then dried to provide 4.5 g. of the white powder of ampicillin.α-benzoyloxybenzyl ester hydrochloride having a melting point of 145—146°C. (decomposed) with a yield of 74.8%.

Infrared absorption spectra:
νNH_3^+ 3350, 3200 cm.$^{-1}$; νNH_2^+ 2700—2600 cm.$^{-1}$
$\nu C=O$ 1780 cm.$^{-1}$ (lactam), 1750—1740 cm.$^{-1}$ (ester), 1680 cm.$^{-1}$ (amide).

Elementary analysis as $C_{30}H_{30}N_3O_6SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	60.45	5.07	7.05	5.95
Found:	60.16	5.60	6.89	6.20.

Example 11.

In 60 ml. of dimethylformamide was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 3.0 g. of potassium bicarbonate and 8.2 g. of 1-(phenylacetoxy)butyl bromide, the mixture was stirred for 16 hours at room temperature. Then, the mixture was processed as in Example 9 to provide 10.3 g. of viscous benzylpenicillin.1-(phenylacetoxy)butyl ester with a yield of 65.3%.

Infrared absorption spectra:
νNH 3300 cm.$^{-1}$
$\nu C=O$ 1780 cm.$^{-1}$ (β-lactam), 1760 cm.$^{-1}$, 1740 cm.$^{-1}$ (ester), 1670 cm.$^{-1}$ (amide).

Example 12.

In 50 ml. of dichloromethane was dissolved 5.3 g. of benzylpenicillin 1-(phenylacetoxy)butyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C. The, after adding 2.3 g. of phosphorus pentachloride, the mixture was stirred for 1.5 hours at −25°C.±5°C. Then, 40 ml. of methanol was added dropwise to the mixture at the same temperature and the mixture and further stirred for 2 hours to provide an iminoether solution.

After adding to the solution 6.86 ml. of N,N-dimethylaniline, 2.5 g. of D(−)-α-phenylglycylchloride.hydrochloride was added to the mixture slowly over a one hour period with stirring at −25±5°C. Thereafter, the mixture was stirred for further 2 hours at the same temperature and then the reaction mixture was processed as in Example 10 to provide 3.95 g. of the white powder of aminicillin.1-(phenylacetoxy)butyl ester having a melting point of 135—138°C. (decomposed) with a yield of 67.9%.

Infrared absorption spectra:
νNH_3^+ 3400 cm.$^{-1}$, 3200 cm.$^{-1}$
νNH_2^+ 2700—2600 cm.$^{-1}$
$\nu C=O$ 1780—1740 cm.$^{-1}$ broad (β-lactam, ester), 1680 cm.$^{-1}$ (amide).

Elementary analysis as $C_{28}H_{34}N_3O_6SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	58.38	5.95	7.29	6.15
Found:	58.07	6.46	7.11	6.33.

Example 13.

In 60 ml. of dimethylformamide was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 3.0 g. of potassium bicarbonate and 7.8 g. of α-(butyryloxy)benzyl bromide, the mixture was stirred for 16 hours at room temperature.

The mixture was processed as in Example 9 to provide 11.7 g. of oily benzylpenicillin-α-(butyryloxy)benzyl ester with a yield of 76.2%.

Infrared absorption spectra:
νNH 3300 cm.$^{-1}$
$\nu C=O$ 1790—1760 cm.$^{-1}$ broad (β-lactam, ester) 1740 cm.$^{-1}$ (ester), 1660 cm.$^{-1}$ (amide).

Example 14.

In 50 ml. of dichloromethane was dissolved 5.1 g. of benzylpenicillin-α-(butyryloxy)benzyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C.

After adding 2.3 g. of phosphorus pentachloride, the mixture was stirred for 1.5 hours at −25±5°C. Then, 40 ml. of methanol was added dropwise to the mixture at the same temperature, the resultant mixture was stirred for further 2 hours to provide an iminoether solution.

After adding to the solution 6.86 ml. of N,N-dimethylaniline, 2.5 g. of D(−)-α-phenylglycylchloride hydrochloride was added to the solution slowly over a one hour period with stirring at −25±5°C. Thereafter, the resultant mixture was stirred for 2 hours at the same temperature and then the reaction mixture was processed as in Example 10 to provide 3.8 g. of the white powder of ampicillin.α-(butyryloxy)benzyl ester hydrochloride having a melting point of 128—130°C. (decomposed) with a yield of 67.7%.

Infrared absorption spectra:
νNH_3^+ 3350 cm.$^{-1}$, 3150 cm.$^{-1}$
νNH_2^+ 2700—2600 cm.$^{-1}$
$\nu C=O$ 1780 cm.$^{-1}$ (β-lactam), 1760—1750 cm.$^{-1}$ (ester), 1680 cm.$^{-1}$ (amide).

Elementary analysis as $C_{27}H_{32}N_3O_6SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	57.70	5.74	7.48	6.31
Found:	57.51	5.97	7.35	6.20.

Example 15.

In 60 ml. of dimethylformamide was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 3.0 g. of potassium bicarbonate and 6.8 g. of 1-cyclohexylcarbonyloxyethyl bromide, the mixture was stirred for 16 hours at room temperature.

By treating the product as in Example 9, 11 g. of oily benzylpenicillin 1-cyclohexylcarbonyloxyethyl ester was obtained with a yield of 74.9%.

Infrared absorption spectra:
νNH 3300 cm.$^{-1}$
$\nu C=O$ 1780 cm.$^{-1}$ (β-lactam) 1760 cm.$^{-1}$, 1740 cm.$^{-1}$ (ester), 1660 cm.$^{-1}$ amide).

Example 16.

In 50 ml. of dichloromethane was dissolved 4.9 g. of benzylpenicillin 1-cyclohexylcarbonyloxyethyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline,

the mixture was cooled to −25°C. Then, after adding 2.3 g. of phosphorus pentachloride, the resultant mixture was stirred for 1.5 hours at −25±5°C. Then, 40 ml. of methanol was added dropwise to the mixture at the same temperature and the resultant mixture was further stirred for 2 hours to provide an iminoether solution.

To the solution was added 6.86 ml. of N,N-dimethylaniline and then 2.5 g. of D-(−)-α-phenylglycyl chloride.hydrochloride was further added slowly to the mixture over a one hour period with stirring at −25±5°C.

Then, after stirring the mixture for 2 hours at the same temperature, the reaction mixture was mixed with 50 ml. of cold and saturated aqueous sodium chloride solution followed by stirring for 0.5 hour at a temperature of −5°C. to 0°C. The dichloromethane layer thus formed was recovered, washed with 30 ml. of 0.5 *N* hydrochloric acid saturated with sodium chloride and then 30 ml. of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at low temperature to provide an oily residue. The residue was dissolved in a mixture of 50 ml. of cold water and 20 ml. of ethyl acetate with stirring and then the aqueous layer thus formed was recovered. The aqueous layer was washed with 20 ml. of ethyl acetate and then mixed with a small amount of activated carbon followed by filtration. On the filtrate was added in layer 30 ml. of ethyl acetate and then sodium chloride was added to the mixture with stirring to saturate the system. The ethyl acetate layer thus formed was recovered and further the aqueous layer thus separated was extracted twice each with 20 ml. of ethyl acetate. The ethyl acetate extracts were combined with the ethyl acetate layer recovered above and the mixture was washed with 30 ml. of cold saturated aqueous sodium choride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at low temperature. The residue was mixed with ether and the crystal thus formed was recovered by filtration, washed with a small amount of petroleum ether, and dried to provide 3.6 g. of the white powder of ampicillin 1-cyclohexylcarbonyloxyethyl ester having a melting point of 134—137°C. (decomposed) with a yield of 66.5%.

Infrared absorption spectra:
νNH_3^+ 3350 cm.$^{-1}$, 3150 cm.$^{-1}$ νNH_2^+ 2700 cm.$^{-1}$
$\nu C=O$ 1780 cm.$^{-1}$ (β-lactam), 1755 cm.$^{-1}$, 1740 cm.$^{-1}$ (ester) 1680 cm.$^{-1}$ (amide)

Elementary analysis as $C_{25}H_{34}N_3O_6SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	55.60	6.35	7.78	6.56
Found:	55.17	6.82	7.50	6.25.

Example 17.

In 60 ml. of dimethylformamide was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 3 g. of potassium bicarbonate and 6.9 g. of 1-benzoyloxyethyl bromide, the mixture was stirred for 16 hours at room temperature.

The reaction mixture thus obtained was dispersed in 100 ml. of ice-water and then extracted thrice each with 50 ml. of ethyl acetate. The ethyl acetate extracts were combined each other and the mixture was washed with 50 ml. of 5% aqueous sodium bicarbonate solution and then 50 ml. of water, mixed with activated carbon followed by filtration, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at a low temperature. The residue was washed with a small amount of n-hexane and dried under a reduced pressure to provide 10 g. of viscous benzylpenicillin 1-benzoyloxyethyl ester with a yield of 68.9%.

Infrared absorption spectra:
νNH 3300 cm.$^{-1}$, $\nu C=O$ 1780—1750 cm.$^{-1}$ broad (β-lactam.ester), 1735 cm.$^{-1}$ (ester), 1660 cm.$^{-1}$ (amide).

Example 18.

In 50 ml. of dichloromethane was dissolved 4.8 g. of benzylpenicillin 1-benzoyloxyethyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C. After adding 2.3 g. of phosphorus pentachloride, the mixture was stirred for 1.5 hours at −25±5°C. Then, 40 ml. of methanol was added dropwise to the mixture at the same temperature and the mixture was further stirred for 2 hours to provide an iminoether solution.

Then, 6.86 ml. of N,N-dimethylaniline was added to the solution prepared above and further 2.5 g. of D(−)-α-phenylglycylchloride hydrochloride was added slowly to the solution over a one hour period with stirring at −25±5°C.

Then, after stirring the mixture for 2 hours at the same temperature, the reaction mixture was mixed with 50 ml. of cold saturated aqueous sodium chloride solution followed by stirring for 0.5 hour at a temperature of −5°C. to 0°C. Then, the dichloromethane layer thus formed was recovered, washed with 30 ml. of 0.5 *N* aqueous hydrochloric acid solution saturated with sodium chloride and then 30 ml. of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at a low temperature to provide an oily residue. After adding 50 ml. of n-hexane to the residue, the insoluble material was then dissolved in 50 ml. of cold water and 30 ml. of ethyl acetate with stirring and then the aqueous layer thus formed was recovered. The aqueous layer was washed with 20 ml. of ether and after adding a small amount of activated carbon, the mixture was filtered. To the filtrate was added in layer 30 ml. of ethyl acetate and sodium chloride was added thereto to saturate with stirring. Then, the ethyl acetate layer thus formed was recovered and the aqueous layer thus separated was further extracted twice each with 20 ml. of ethyl acetate. The ethyl acetate extracts were combined with the ethyl acetate layer recovered above and the mixture was washed with 30 ml of cold and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate and concentrated under a reduced pressure at a low temperature. The residue thus obtained was mixed with n-hexane and the crystal thus formed was recovered by filtration, washed with a small amount of petroleum ether and dried to provide 3.65 g. of the white powder at ampicillin 1-benzoyloxyethyl ester having a melting point of 137—138°C. (decomposed) with a yield of 68.7%.

Infrared absorption spectra:
νNH_3^+ 3400 cm.$^{-1}$, 3200 cm.$^{-1}$
νNH_2^+ 2700—2600 cm.$^{-1}$
$\nu C=O$ 1780 cm.$^{-1}$ (β-lactam), 1760—1735 cm.$^{-1}$ (ester), 1685 cm.$^{-1}$ (amide).

Elementary analysis as $C_{25}H_{28}N_3O_6SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	56.23	5.28	7.87	6.64
Found:	56.08	5.70	7.57	6.60.

Example 19.

In 60 ml. of dimethylformamide was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 3.0 g. of potassium bicarbonate and 8.0 g. of 1-(phenoxyacetoxy)ethyl bromide, the mixture was stirred for 16 hours at room temperature. By treating the mixture thus obtained as in Example 9, 10.6 g. of oily benzylpenicillin 1-(phenoxyacetoxy)-ethyl ester was obtained with a yield of 68.8%.

Infrared absorption spectra:
νNH 3420 cm.$^{-1}$
$\nu C=O$ 1790 cm.$^{-1}$ (β-lactam), 1765 cm.$^{-1}$, (1740 cm.$^{-1}$ (ester), 1685 cm.$^{-1}$ (amide).

Example 20.

In 50 ml. of dichloromethane was dissolved 5.13 g. of benzylpenicillin.1-(phenoxyacetoxy)ethyl ester and after adding 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C.

Then, after adding 2.3 g. of phosphorus pentachloride, the mixture was stirred for 1.5 hours at −25±5°C. Then, 40 ml. of methanol was added dropwise to the mixture at the same temperature and the resultant mixture was further stirred for 2 hours to provide an iminoether solution.

Then, 6.86 ml. of N,N-dimethylaniline was added to the solution and further 2.5 g. of D(−)-α-phenylglycylchloride-hydrochloride was added to the mixture slowly over one hour period with stirring at −25±5°C.

Then, After stirring the mixture for 2 hours at the same temperature, the reaction mixture was processed as in Example 18 to provide 3.5 g. of the white powder of ampicillin.1-(phenoxyacetoxy)ethyl ester hydrochloride having a melting point of 116—119°C (decomposed) with a yield of 61.7%.

Infrared absorption spectra:
νNH_3^+ 3350 cm.$^{-1}$, 3200 cm.$^{-1}$
νNH_2^+ 2700—2600 cm.$^{-1}$
$\nu C=O$ 1790—1745 cm.$^{-1}$ broad (β-lactam, ester), 1690 cm.$^{-1}$ (amide).

Elementary analysis as $C_{26}H_{30}N_3O_7SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	55.36	5.36	7.45	6.29
Found:	55.04	5.74	7.29	6.40.

Example 21.

In 100 ml. of dimethylformamide was suspended 13.2 g. of benzylpenicillin potassium salt and after adding to the suspension 3 g. of potassium bicarbonate and 11 g. of 1-acetoxy-3-phenylpropyl bromide, the mixture was stirred for 16 hours at room temperature.

The reaction mixture was dispersed in 150 ml. of ice-water and the mixture was processed as in Example 9 to provide 16 g. of oily benzylpenicillin.1-acetoxy-3-phenylpropyl ester with a yield of 88.4%.

Infrared absorption spectra:
νNH 3320 cm.$^{-1}$
$\nu C=O$ 1790—1730 cm.$^{-1}$ broad (β-lactam, ester) 1660 cm.$^{-1}$ (amide).

Example 22.

In 50 ml. of dichloromethane was dissolved 5.62 g. of benzylpenicillin.1-acetoxy-3-phenylpropyl ester tand after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to −25°C.

After adding further 2.3 g. of phosphorus pentachloride, the mixture was stirred for 1.5 hours at −25±5°C. Then, 40 ml. of methanol yas added dropwise to the mixture at the same temperature, the mixture was further stirred for 2 hours to provide an iminoether solution.

Then, 6.86 ml. of N,N-dimethylaniline was added to the solution and further 2.5 g. of D(−)-α-phenylglycylchloride.hydrochloride was added slowly to the mixture over a one hour period with stirring at −25±5°C.

After stirring the mixture for 2 hours at the same temperature, the reaction mixture was mixed with 50 ml. of cold and saturated aqueous sodium chloride solution followed by stirring for 0.5 hour at a temperature of −5°C. to 0°C. The dichloromethane layer thus formed was recovered, washed with 30 ml. of 0.5 *N* aqueous hydrochloric acid solution saturated with sodium chloride and then 30 ml. of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at low temperature to provide an oily residue. When 50 ml. of ether was added to the residue followed by stirring, the system was solidified. The solidified material was dissolved in 50 ml. of ice-water and washed twice each with 30 ml. of ether. Onto the aqueous layer thus formed was added in layer 30 ml. of ethyl acetate and then sodium chloride was added thereto with stirring to saturate with it. Then, the ethyl acetate layer was recovered and the aqueous layer thus separated was extracted twice each with 20 ml. of ethyl acetate. The ethyl acetate extracts were combined with the ethyl acetate layer thus recovered and the mixture was washed with 30 ml. of cold and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at low temperature. The residue was dissolved in a small amount of ethyl acetate and then ether was added to the solution to reprecipitate the product. The crystal was filtered, washed with a small amount of petroleum ether, and dried to provide 3.3 g. of the white powder of ampicillin 1-acetoxy-3-phenylpropyl ester hydrochloride having a melting point of 118—122°C. (decomposed) with a yield of 53.3%.

Infrared absorption spectra:
νNH_3^+ 3400 cm.$^{-1}$, 3200 cm.$^{-1}$
νNH_2^+ 2700—2600 cm.$^{-1}$
$\nu C=O$ 1780 cm.$^{-1}$ (β-lactam), 1760—1740 cm.$^{-1}$ (ester), 1680 cm.$^{-1}$ (amide).

Elementary analysis as $C_{27}H_{32}N_3O_6SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	57.67	5.74	7.48	6.31
Found:	57.28	6.12	7.18	6.55

Example 23.

In 50 ml. of dimethylformamide was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 0.7 g. of potassium bicarbonate, 6.9 g. of 1-acetoxy-2,2,2-trichloroethyl bromide was added dropwise to the mixture over a period of 25 minutes with stirring. After stirring the mixture further for 2 hours at room temperature, the reaction mixture was dispersed in 50 ml. of ice-water and then extracted thrice each with 50 ml. of ethyl acetate. The ethyl acetate extracts were combined and the mixture was washed with 50 ml. of 5% aqueous sodium bicarbonate solution and then 50 ml. of water, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure at low temperature. The residue was mixed with 75 ml. of ether with stirring and the insoluble matters were separated by decantation. To the ether solution was added 100 ml. of petroleum ether with stirring and the oily material thus formed was separated by decantation and dried under reduced pressure to provide 9.8 g. of powder benzylpenicillin 1-acetoxy-2,2,2-trichloroethyl ester with a yield of 62.2%.

Infrared absorption spectra:
νNH 3300 cm.$^{-1}$
νC=O 1780—1860 cm.$^{-1}$ broad (β-lactam, ester), 1660 cm.$^{-1}$ (amide).

Example 24.

In 50 ml. of dichloromethane was dissolved 5.24 g. of benzylpenicillin.1-acetoxy-2,2,2-trichloroethyl ester and after adding to the solution 4.12 ml. of N,N-dimethylaniline, the mixture was cooled to $-25°$C. After adding 2.3 g. of phosphorus pentachloride, the mixture was stirred for 1.5 hours at $-25\pm5°$C. Then, 40 ml. of methanol was added dropwise to the mixture at the same temperature, the resultant mixture was stirred for further 2 hours to provide an iminoether solution.

Then, 6.86 ml. of N,N-dimethylaniline was added to the solution prepared above and further 2.5 g. of D(−)-α-phenylglycylchloride.hydrochloride was added to the mixture slowly over a one hour period with stirring at $-25\pm5°$C.

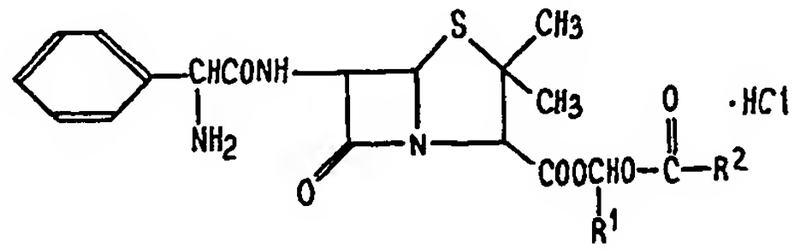
Then, after stirring the mixture for 2 hours at the same temperature, the reaction mixture was mixed with 50 ml. of cold and saturated aqueous sodium chloride solution and the mixture was stirred for 0.5 hour at a temperature of from $-5°$C. to 0°C. Then, the dichloroethane layer thus formed was recovered, washed with 30 ml. of 0.5 *N* aqueous hydrochloric acid solution and then 30 ml. of saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at low temperature to provide an oily residue. The residue was dissolved in 50 ml. of ethyl acetate and then n-hexane was added to the solution, whereby an oily product was formed. The oily product was recovered by decantation, dried under reduced pressure, mixed with 50 ml. of water, and mixed with a small amount of activated carbon. The mixture was stirred for 30 minutes at room temperature and filtered. To the filtrate was added in layer 30 ml. of ethyl acetate, and sodium chloride was added thereto with stirring to saturate with it. Then, the ethyl acetate layer thus formed was recovered and the aqueous layer was extracted twice each with 20 ml. of ethyl acetate. The ethyl acetate layer and extracts were combined and the mixture was washed with 30 ml. of cold and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at low temperature. The residue prepared was dissolved in a mixture of 10 ml. of benzene and 3 ml. of ethyl acetate and after filtering away the insoluble matters, petroleum ether was added to the filtrate, whereby white precipitates were formed. The precipitates were recovered by filtrations, washed with a small amount of petroleum ether, and dried to provide 3.06 g. of the white powder of ampicillin.1-acetoxy-2,2,2-trichloroethyl ester having a melting point of 148—149°C. (decomposed) with a yield of 53.4%,

Infrared absorption spectra:
νNH_3^+ 3400 cm.$^{-1}$, 3200 cm.$^{-1}$
νNH_2^+ 2700—2600 cm.$^{-1}$
νC=O 1790—1760 cm.$^{-1}$ broad (β-lactam, ester) 1680 cm.$^{-1}$ (amide).

Elementary analysis as $C_{20}H_{23}N_3O_6SCl_4$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	41.76	4.03	7.30	24.65
Found:	41.30	4.51	7.05	25.24.

Also, by the similar ways as above, the compounds represented by the following formula and in the following table were prepared, the results of which are also shown in the same table:



TABLE

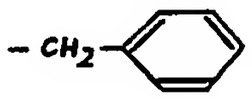
Example Number	R^2	R^1	Melting point (°C)	Elementary analysis							
				Found				Calculated			
				C(%)	H(%)	N(%)	Cl(%)	C(%)	H(%)	N(%)	Cl(%)
25	$-CH_2CH_3$	$-CH_3$	107–110	51.48	6.24	8.37	7.05	51.90	5.81	8.65	7.30
26	$-(CH_2)_6CH_3$	$-CH_3$		55.89	7.14	7.28	6.41	56.15	6.89	7.56	6.37
27	$-CH(C_2H_5)_2$	$-CH_3$	88–107	54.24	6.80	7.56	6.83	54.59	6.49	7.96	6.71
28		$-CH_3$	150–152	56.90	5.86	7.26	6.64	56.98	5.52	7.67	6.47
29	$-CH_2CH_3$	$-CH_2CH_3$	100–104	52.63	6.49	8.22	7.18	52.85	6.05	8.40	7.09
30	$-(CH_2)_2CH_3$	$-CH_2CH_3$	113–120	53.40	6.45	7.97	6.80	53.74	6.27	8.17	6.90
31	$-CH(CH_3)_2$	$-CH_2CH_3$	130–136	53.31	6.56	8.05	6.96	53.74	6.27	8.17	6.90
32	$-C(CH_3)_3$	$-CH_2CH_3$	125–128	54.14	6.77	7.52	6.88	54.59	6.49	7.96	6.71
33	$-CH(CH_2CH_3)_2$	$-CH_2CH_3$	105–108	55.05	6.87	7.57	6.60	55.39	6.69	7.75	6.54
34	$-CH_3$	$-(CH_2)_2CH_3$	95–99	52.34	6.48	8.21	7.18	52.85	6.05	8.40	7.09
35	$-CH_2CH_3$	$-(CH_2)_2CH_3$	122–126	53.30	6.56	8.02	7.14	53.74	6.27	8.17	6.90
36	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	122–123	54.13	6.83	7.64	6.60	54.59	6.49	7.96	6.71
37	$-CH(CH_3)_2$	$-(CH_2)_2CH_3$	106–110	54.19	6.66	7.53	6.54	54.59	6.49	7.96	6.71
38	$-(CH_2)_6CH_3$	$-(CH_2)_2CH_3$	105–110	57.12	7.58	6.98	6.24	57.57	7.25	7.19	6.07
39	$-C(CH_3)_3$	$-(CH_2)_2CH_3$	111–115	55.02	6.91	7.50	6.67	55.39	6.69	7.75	6.54

TABLE (Continued)

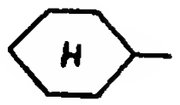
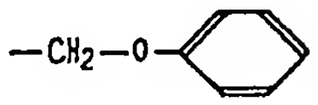
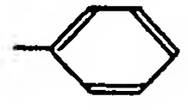
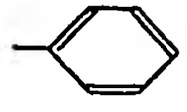
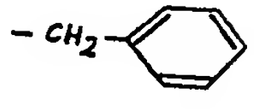
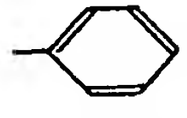
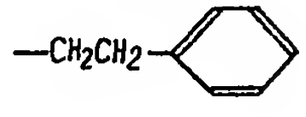
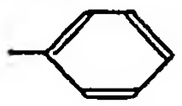
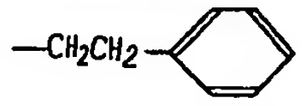
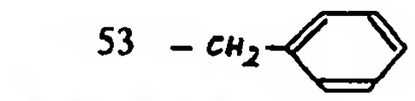
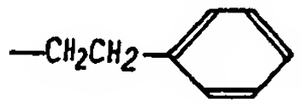
Example Number	R^2	R^1	Melting point (°C)	Elementary analysis							
				Found				Calculated			
				C(%)	H(%)	N(%)	Cl(%)	C(%)	H(%)	N(%)	Cl(%)
40	$-CH(CH_2CH_3)_2$	$-(CH_2)_2CH_3$	85–104	55.88	7.15	7.30	6.59	56.15	6.89	7.56	6.37
41		$-(CH_2)_2CH_3$	127–130	56.70	6.87	7.03	6.44	57.08	6.74	7.40	6.24
42		$-(CH_2)_2CH_3$	117–120	56.35	6.12	7.00	6.12	56.80	5.79	7.10	5.99
43	$-CH_3$	$-CH(CH_3)_2$	115–119	52.48	6.55	8.17	6.90	52.85	6.05	8.40	7.09
44	$-CH_2CH_3$	$-CH(CH_3)_2$	126–128	53.29	6.60	8.02	6.87	53.74	6.27	8.17	6.90
45	$-CH(CH_3)_2$	$-CH(CH_3)_2$	124–126	54.17	6.85	7.59	6.95	54.59	6.49	9.96	6.71
46	$-C(CH_3)_3$	$-CH(CH_3)_2$	127–130	55.10	6.94	7.51	6.68	55.39	6.69	7.75	6.54
47	$-CH_3$	$-(CH_2)_5CH_3$	108–112	54.87	6.99	7.44	6.32	55.39	6.69	7.75	6.54
48	$-CH_3$			55.86	5.69	7.48	6.81	56.23	5.28	7.87	6.64
49	$-C(CH_3)_3$		143–144	58.31	6.32	7.00	6.10	58.38	5.95	7.29	6.15
50			128–130	60.73	5.68	6.79	5.72	61.03	5.29	6.89	5.81
51	$-C(CH_3)_3$			59.25	6.87	6.38	5.95	59.64	6.34	6.95	5.81

TABLE (Continued)

Example Number	R^2	R^1	Melting point (°C)	Elementary analysis							
				Found				Calculated			
				C(%)	H(%)	N(%)	Cl(%)	C(%)	H(%)	N(%)	Cl(%)
52			136–140	61.22	5.90	6.46	5.83	61.58	5.49	6.73	5.68
53			105–110	61.87	5.89	6.24	5.39	62.11	5.69	6.58	5.56

Example 53A.

In 120 ml. of acetone was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 5.1 g. of 1-pivaloyloxyethyl chloride and 3 ml. of 25% aqueous sodium iodide, the mixture was refluxed for 5 hours. After cooling, the reaction mixture was filtered and the filtrate was concentrated under a reduced pressure. The residue was washed with 30 ml. of petroleum ether, dissolved in 80 ml. of ethyl acetate and the solution prepared was filtered. The ethyl acetate solution was washed with 50 ml. of 5% aqueous sodium bicarbonate solution and then 50 ml. of water, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure. The concentrate was subjected to a silica gel column chromatography followed by elution by a benzene-ethyl acetate (3:1 in volume ratio) solvent and the eluate was concentrated under a reduced pressure to provide 8.5 g. of benzylpenicillin.1-pivaloyloxyethyl ester.

Example 54.

In 25 ml. of chloroform was dissolved 5.0 g. of benzylpenicillin.1-pivaloyloxyethyl ester and then a chloroform solution containing 1.5 g. of perbenzoic acid was added slowly to the solution with stirring under ice-cooling. Then, after stirring the mixture for 10 minutes at room temperature, the mixture was washed twice each with an aqueous sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and then the solvent was distilled away to provide 4.9 g. of amorphous benzylpenicillin-sulfoxide.1-pivaloyloxyethyl ester.

The infrared absorption spectra and the NMR spectra of the product coincided with those of the structure. Furthermore, the NMR spectra of it suggested the presence of the stereoisomer formed by the difference in the steric structure of the ester residual group.

Elementary analysis as $C_{23}H_{30}N_2O_7S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	57.73	6.32	5.85	6.70
Found:	57.81	6.53	5.67	6.53

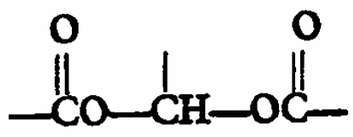
Example 55.

In 24 ml. of anhydrous dioxane was dissolved 4.8 g. of benzylpenicillinsulfoxide. 1-pivaloyloxyethyl ester and after adding to the solution 123 mg. of phenyl dihydrogen phosphate.mono-hydrate and 57 μl. of absolute pyridine, the mixture was heated for 4 hours to 105°C. to provide an orange-yellow reaction mixture. The solvent was distilled away under a reduced pressure and the residue thus obtained was dissolved in benzene. The solution was subjected to a silica gel column chromatography and the product was developed and eluted with a mixture of benzene and ethyl acetate (10:1 in volume ratio). By distilling away the solvent from the faint yellow eluate under a reduced pressure, 3.7 g. of the faint yellow powder of 7-phenylacetamidodesacetoxycephalosporanic acid 1-pivaloyloxyethyl ester was obtained.

The nuclear magnetic resonance spectra of the product well coincided with the structure.

Nuclear magnetic resonance spectra ($CDCl_3$ solution):

δ: 1.22 (9H, singlet, $-(CH_3)_3$), 1.51 (3H, doublet, J = 5.5 Hz, CH_3), 2.09 (3H, singlet, CH_3), 2.90, 3.20, 3.31, 3.61 AB pattern (2H, $-S-CH_2-$), 3.6 (2H, singlet, $-CH_2-$), 4.88 (1H, doublet, J = 4Hz, lactam), 5.69 (1H, quartet, J = 4Hz, 8.5 Hz, lactam), 6.48 (1H, doublet, J = 8.5 Hz, NH), 6.95 (1H, quartet, J = 5.5 Hz,



), 7.30 (5H, singlet, aromatic H).

Elementary analysis as $C_{23}H_{28}N_2O_6S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	59.98	6.13	6.08	6.96
Found:	59.85	6.27	6.01	6.73.

Example 56.

In 42 ml. of chloroform was dissolved 8.4 g. of benzylpenicillin.1-acetoxyethyl ester and then a chloroform solution containing 2.76 g. of perbenzoic acid was added slowly to the solution with stirring under ice-cooling.

Then, by processing the mixture as in Example 54, 8.2 g. of amorphous benzylpenicillinsulfoxide 1-acetoxyethylester was obtained. The infrared absorption spectra and the NMR spectra of the product well conincided with the structure. Furthermore, the NMR spectra suggested the presence of the steroisomer formed by the difference in steric structure of the ester residual group.

Elementary analysis as $C_{20}H_{24}N_2O_7S$:

	C(%)	H(%)	N(%)
Calculated:	55.04	5.54	6.42
Found:	55.19	5.66	6.31

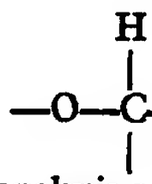
Example 57.

In 40 ml. of dioxane was dissolved 7.0 g. of benzylpenicillinsulfoxide 1-acetoxyethyl ester and after adding to the solution 195 mg. of phenyl dihydrogen phosphate. mono-hydrate and 91 μl. of pyridine, the mixture was refluxed. The refluxing procedure was so conducted that the dioxane thus distilled was dehydrated by a molecular sieve and recycled into the reaction mixture. After conducting the refluxing for 7 hours, the solvent was distilled away from the reaction mixture under a reduced pressure and the residue obtained was dissolved in benzene. Then, the solution was subjected to a silica

gel column chromatography and the product was developed by a mixture of benzene and ethyl acetate (10:1 in volume ratio). By distilling away the main fraction of the eluate under a reduced pressure, 5.2 g. of the faint yellow powder of 7-phenylacetamido-desacetoxycephalosporanic acid.1-acetoxyethyl ester was obtained.

NMR spectra of the product ($CDCl_3$ solution):

δ: 1.51 (3H, doublet, J=5.5 Hz, CH_3), 2.09 (3H, singlet, CH_3), 2.13 (3H, singlet, CH_3), 2.97, 3.28, 3.38, 3.70, AB uattern (2H, —S—CH_2), 3.61 (2H, singlet, —CH_2—), 4.92 (1H, doublet, J=4.5 Hz, lactam), 5.76 (1H, quartet, J=4.5 Hz, 9 Hz, lactam), 6.75 (1H, doublet, J=9 Hz, NH), 6.97 (1H, quartet, J=5.5 Hz,



), 7.30 (5H, singlet, aromatic H).

Elementary analysis as $C_{20}H_{22}N_2O_6S$:

	C(%)	H(%)	N(%)
Calculated:	57.40	5.30	6.69
Found:	57.59	5.39	6.44.

Example 58.

In 44 ml. of chloroform was dissolved 8.7 g. of benzylpenicillin.1-acetoxypropyl ester and then a chloroform solution containing 2.76 g. of perbenzoic acid was added slowly to the solution with stirring under ice-cooling. Then, by processing the mixture as in Example 54, 8.5 g. of amorphous benzylpenicillinsulfoxide.1-acetoxypropyl ester was obtained. The infrared absorption spectra and NMR spectra of this product well coincided with the structure. Furthermore, the NMR spectra suggested the presence of the steroisomer formed by the difference in the steric structure of the ester residual group.

Elementary analysis as $C_{21}H_{26}N_2O_7S$:

	C(%)	H(%)	N(%)
Calculated:	55.99	5.82	6.22
Found:	56.11	5.88	6.15.

Example 59.

In 25 ml. of anhydrous dioxane was dissolved 4.4 g. of benzylpenicillinsulfoxide. 1-acetoxypropyl ester and after adding to the solution 122 mg. of phenyl dihydrogen phophate mono-hydrate and 57 μl. of pyridine, the mixture was refluxed under heating as in Example 57. Then, by processing the product as in Example 57, 3.4 g. of the faint yellow powder of 7-phenylacetamidodesacetoxycephalosporanic acid.1-acetoxypropyl ester was obtained.

The NMR spectra of the product ($CDCl_3$ solution):

δ: 0.98 (3H, triplet, J=7 Hz, CH_3), 1.78 (2H, multiplet, CH_2), 2.09 (3H, singlet, CH_3), 2.14 (3H, singlet, CH_3), 2.93, 3.25, 3.35, 3.65, AB pattern (2H, —SCH_2—), 3.62 (2H, singlet, —CH_2—), 4.90 (1H, doublet, 4.5 Hz, lactam), 5.72 (1H, quartet, j=4.5 Hz, 9 Hz, lactam), 6.5 (1H, doublet, J=9 Hz, NH), 6.81 (1H, triplet

J=5.5 Hz, —O—CH—O—), 7.28 (5H, singlet, aromatic H).

Elementary analysis as $C_{21}H_{24}N_2O_8S$:

	C(%)	H(%)	N(%)
Calculated:	58.32	5.59	6.48
Found:	58.42	5.51	6.38.

The product could further be separated by a silica gel column chromatography into two stereoisomeric sets of crystals formed by the steric structure of the ester residual group. The isomer sparingly soluble in ether has a melting point of 144—146°C. and $[\alpha]_D^{20} = +33.9$ (C=1, $CHCl_3$), while the isomer soluble in ether had a melting point of 151—154°C. and $[\alpha]_D^{20} = +47.9$ (C=1, $CHCl_3$).

Example 60.

a). In 50 ml. of chloroform was dissolved 10 g. of benzylpenicillin 1-propionyloxyethyl ester and after adding to the solution slowly a chloroform solution of 3.2 g. of perbenzoic acid with stirring under ice-cooling, the mixture was stirred for 10 minutes at room temperature. The reaction mixture was washed twice each with aqueous sodium bicarbonate solution and then water and dried over anhydrous magnesium sulfate. Then, by distilling away the solvent therefrom under a reduced pressure, 10.1 g. of amorphous benzylpenicillinsulfoxide 1-propionyloxyethyl ester was obtained.

b). In 50 ml. of absolute dioxane was dissolved 9.0 g. of benzylpenicillinsulfoxide 1-propionyloxyethyl ester and after adding to the solution 244 mg. of phenyl dihydrogen phosphate monohydrate and 114 μl. of pyridine, the mixture was heated for 7 hours to 105°C. The solvent was then distilled away from the pale brown reaction mixture under a reduced pressure and the residue thus obtained was dissolved in benzene. The solution was washed twice with water, dried over anhydrous magnesium sulfate, and subjected to a silica gel column chromatography followed by elution with a mixture of benzene and ethyl acetate (10:1 in volume ratio). Then by distilling away the solvent from the faint yellow eluate under a reduced pressure, 6.8 g. of the faint yellow powder of 7-phenylacetamidodesacetoxycephalosporanic acid.1-propionyloxyethyl ester was obtained.

$[\alpha]_D^{18} = +42.8$ (C = 1, chloroform)

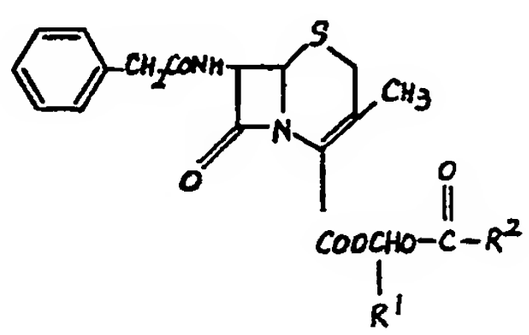
Elementary analysis as $C_{21}H_{24}N_2O_6S$:

Calculated: N 6.48%
Found: N 6.42%.

Nuclear magnetic resonance spectra ($CDCl_3$ solution):

δ: 1.12 (3H, triplet, J = 7.5 Hz, $-CH_3$), 1.51 (3H, doublet, J = 5.3 Hz, $-CH_3$), 2.10 (3H, singlet, CH_3), 2.37 (2H, quartet, J = 7.5 Hz, $-CH_2-$), 2.95, 3.27, 3.38, 3.69 (2H, AB pattern, $-S-CH_2-$), 3.61 (2H, singlet, $-CH_2-$), 4.91 (1H, doublet, J = 5 Hz, lactam), 6.62 (1H, doublet, J = 9 Hz, NH), 7.02 (1H, triplet, J = 5.5 Hz, $-\underset{|}{CH}-$), 7.30 (5H, singlet, aromatic H).

Furthermore, by following the similar procedures as in Examples 54—60, the compounds represented by the following formula were prepared, the yields and the properties of which are shown in the following table together with the structures of the compounds.



TABLE

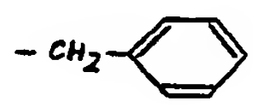
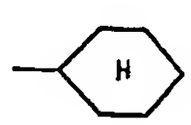
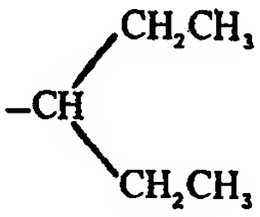
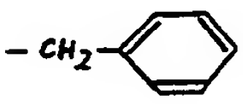
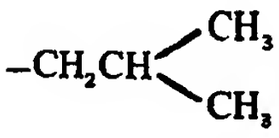
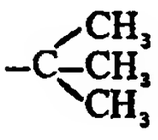
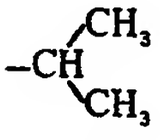
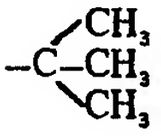
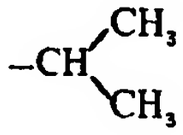
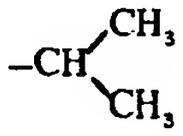
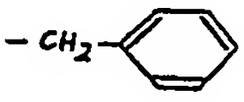
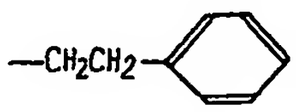
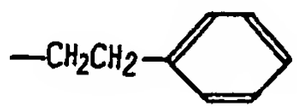
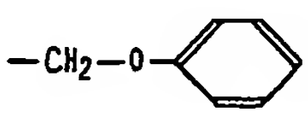
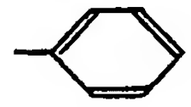
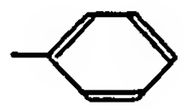
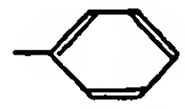
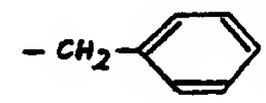
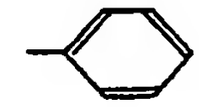
Example Number	R^2	R^1	$[\alpha]_D^{18}$ (c = 1, chloroform)	Yield (%)	Elementary analysis Calculated N(%)	Found N(%)
61		$-CH_2CH_3$	+ 33.2	69	5.50	5.30
62	$-CH_2CH_3$	$-CH_2CH_3$	–	60	6.27	6.03
63	$-CH_2CH_3$	$-CH_2CH_2CH_3$	+ 40.8	62	6.08	5.94
64		$-CH_2CH_2CH_3$	+ 29.1	85	5.44	5.12
65	$-CH_3$	$-CH_2CH_2CH_3$	+ 41.0	72	6.27	6.22
66	$-(CH_2)_6CH_3$	$-CH_2CH_2CH_3$	+ 36.0	77	5.28	5.07
67		$-CH_2CH_2CH_3$	+ 35.4	81	5.57	5.52
68	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$	+ 39.9	72	5.90	5.72
69		$-CH_2CH_2CH_3$	+ 38.2	79	5.36	5.39
70		$-CH_2CH_2CH_3$	+ 43.2	90	5.73	5.40
71	$-(CH_2)_3CH_3$	$-CH_2CH_2CH_3$	+ 45.6	77	5.73	5.56
72		$-CH_2CH_2CH_3$	+ 34.8	81	5.73	5.52
73		$-CH_2CH_2CH_3$	–	75	5.90	5.67
74			+ 31.8	77	5.73	5.51
75	$-CH_2CH_3$		+ 51.1	64	6.08	6.14
76		$-(CH_2)_5CH_3$	+ 36.0	82	4.96	4.73
77	$-CH_2CH_3$	$-(CH_2)_5CH_3$	+ 43.2	70	5.57	5.53

TABLE (Continued)

Example Number	R^2	R^1	$[\alpha]_D^{18}$ (c=1, chloroform)	Yield (%)	Elementary analysis Calculated N(%)	Found N(%)
78	$-CH_3$		+33.4	78	5.50	5.62
79	$-CH_2CH_3$		+35.6	71	5.36	5.44
80	$-CH_2CH_3$	$-CCl_3$	+35.0	28	5.23	5.21
81	$-CH_2CH_2CH_3$		+20.9	63	5.20	5.34
82		$-CH_2CH_2CH_3$	+18.1	49	5.50	5.66
83	$-CH_2CH_3$		+30.2	44	5.66	5.36
84	$-CH_2CH_2CH_3$		+24.9	61	5.50	5.48
85			+27.4	88	5.03	5.05

Example 85A.

a). In 100 ml. of acetone was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 1.5 g. of potassium bicarbonate and 10 g. of 1-acetoxyethyl bromide, the mixture was refluxed under heating for 2 hours. After cooling, the reaction mixture was filtered and the filtrate was concentrated under a reduced pressure. The residue thus formed was washed with 30 ml. of petroleum ether and dissolved in 80 ml. of ethyl acetate followed by filtration. The ethyl acetate solution thus filtered was washed with 50 ml. of 5% aqueous sodium bicarbonate solution and then 50 ml. of water, dried over anhydrous magnesium sulfate, and then concentrated under a reduced pressure. The concentrate was subjected to a chromatography by absorbing on a silica gel packed in a column and developing the product thus adsorbed with a mixture of benzene and ethyl acetate (3:1 in volume ratio) and the eluate was concentrated under a reduced pressure to provide 7.5 g. of the colorless powdery crystal of benzylpenicillin.1-acetoxyethyl ester with a yield of 60%.

b). In 42 ml. of chloroform was dissolved 8.4 g. of benzylpenicillin.1-acetoxyethyl ester and then a chloroform solution containing 2.76 g. of perbenzoic acid was added slowly to the solution with stirring under ice-cooling. Thereafter, the mixture was stirred for 10 minutes at room temperature, washed twice each with aqueous sodium bicarbonate solution and then with water, dried over anhydrous magnesium sulfate, and the solvent of the mixture was distilled away to provide 8.2 g. of amorphous benzylpenicillinsulfoxide 1-acetoxyethyl ester.

The infrared absorption spectra and the NMR spectra of the product coincided completely with the structure.

Elementary analysis as $C_{20}H_{24}N_2O_7S$:

	C(%)	H(%)	N(%)
Calculated:	55.04	5.54	6.42
Found:	55.19	5.66	6.31.

c). In 40 ml. of anhydrous dioxane was dissolved 7.0 g. of benzylpenicillinsulfoxide 1-acetoxyethyl ester and after adding to the solution 195 mg of phenyl primary phosphate monohydrate and 91 μl. of pyridine, the mixture was refluxed. The refluxing procedure was so conducted that the dioxane distilled was dehydrated by a molecular sieve and recycled to the reaction mixture. After conducting the refluxing for 7 hours, the solvent was distilled away from the reaction mixture under a reduced pressure and the residue was dissolved in benzene. The solution was subjected to a silica gel column chromatography. The product was developed by a mixture of benzene and ethyl acetate (10:1 in volume ratio) and by distilling away the solvent from the eluate from the column under a reduced pressure, 5.2 g. of the faint yellow powder of 7-phenylacetamidodesacetoxycephalosporanic acid.1-acetoxyethyl ester was obtained.

Elementary analysis as $C_{21}H_{22}H_2O_6S$:

	C(%)	H(%)	N(%)
Calculated:	57.40	5.30	6.69
Found:	57.59	5.39	6.44.

Example 86.

In anhydrous dichloromethane was dissolved 1.57 g. of 7-phenylacetamidodesacetoxycephalosporanic acid.1-acetoxyethyl ester and after adding to the solution 1.5 g. of dimethylaniline and then 865 mg. of anhydrous phosphorous pentachloride under cooling at a temperature lower than −20°C., the mixture was stirred for 3 hours at a temperature of from −15°C. to −10°C. To the orange-yellow reaction mixture was added dropwise 12 ml. of methanol at a temperature of lower than −20°C., and thereafter the mixture was further stirred for 1.5 hours at a temperature of −20°C. Furthermore, 2.5 g. of dimethylaniline and 930 mg. of D(−)-α-phenylglycylchloride. hydrochloride were added to the product and the mixture was allowed to stand overnight at −20°C. The reaction mixture was mixed with saturated aqueous sodium chloride solution and after shaking the mixture well, the organic layer formed was recovered, dried over anhydrous magnesium sulfate and then the solvent was distilled away under a reduced pressure. The residue was dissolved in water, the solution was washed with ether and saturated with sodium chloride, and then an oily material thus formed was extracted with dichloromethane. The dichloromethane extract was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and the solvent was distilled away under reduced pressure. By adding ether to the residue and allowing stand the mixture, 1.63 g. of the white powder of 7-(α-aminophenylacetamido)desacetoxycephalosporanic acid.1-acetoxyethyl ester hydrochloride having a melting point of 142—143°C. was obtained.

Elementary analysis as $C_{20}H_{24}N_3O_6SCl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	51.11	5.15	8.94	6.82	7.54
Found:	50.96	5.52	8.98	6.54	7.82.

The infrared absorption spectra and the NMR spectra of the product coincided completely with the structure.

Example 87.

In 12 ml. of anhydrous dichloromethane was dissolved 714 mg. of 71phenylacetamidodesacetoxycephalosporanic acid.1-acetoxypropyl ester and after adding to the solution 660 mg. of dimethylaniline and then 390 mg. of anhydrous prosphorus pentachloride under cooling at a temperature of lower than −20°C., the mixture was stirred for 3 hours at a temperature of from −5°C. to −10°C. To the orange-yellow reaction mixture thus obtained was added dropwise 8.0 ml. of methanol at a temperature of lower than −20°C. and thereafter the mixture was further stirred for 1.5 hours at a temperature of from −20°C. to −15°C. Furthermore, 1.1 g. of dimethylaniline and 408 mg. of D(−)-α-phenylglycylchloride.hydrochloride were added to the mixture with stirring at a temperature of lower than −20°C. and the mixture was allowed stand overnight at −20°C. The reaction mixture liquid thus obtained was mixed with saturated aqueous sodium chloride solution and after shaking the mixture well, the mixture was processed as in Example 86 to provide 375 mg. of the white crystalline powder of 7-(α-aminophenylacetamido)desacetoxycephalosporanic acid.1-acetoxypropyl ester hydrochloride having a melting point of 138—140°C.

Elementary analysis as $C_{21}H_{26}N_3O_6SCl$:

	C(%)	H(%)	N(%)	S(%)	Cl(%)
Calculated:	52.12	5.41	8.68	6.63	7.33
Found:	52.05	5.50	8.49	6.35	7.62.

The infrared absorption spectra and the NMR spectra of the product coincided completely with the structure.

Example 87A.

a). In 120 ml. of acetone was suspended 11.2 g. of benzylpenicillin potassium salt and after adding to the suspension 5.1 g. of 1-pivaloyloxyethyl chloride and 3 ml. of 25% aqueous sodium iodide solution, the mixture was refluxed for 5 hours. After cooling, the reaction mixture was processed as in Reference z—a) to provide 8.5 g. of the colorless powdery crystal of benzylpenicillin 1-pivaloyloxyethyl ester.

b). In 25 ml. of chloroform was dissolved 5.0 g. of benzylpenicillin.1-pivaloyloxyethyl ester and then a chloroform solution containing 1.5 g. of perbenzoic acid was added to the solution with stirring under ice-cooling. After the addition of it, the mixture was stirred for 10 minutes, washed twice each with sodium bicarbonate solution and then with water, dried over anhydrous magnesium sulfate, and the solvent was distilled away to provide 4.9 g. of amorphous benzylpenicillin.1-pivaloyloxyethyl ester.

The infrared absorption spectra of the product coincided completely with the structure.

Elementary analysis as $C_{23}H_{30}N_2O_7S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	57.73	6.32	5.85	6.70
Found:	57.81	6.53	5.67	6.53.

c). In 24 ml. of anhydrous dioxane was dissolved 4.8 g. of benzylpenicillinsulfoxide.1-pivaloyloxyethyl ester and after adding to the solution 123 mg. of phenyl dihydrogen phosphate monohydrate and 57 μl. of absolute pyridine, the mixture was heated for 4 hours to 105°C. Then, the solvent was distilled away from the orange-yellow reaction mixture under a reduced pressure and the residue was dissolved in benzene. The solution was subjected to a silica gel column chromatography and then the product thus adsorbed was developed by a mixture of benzene and ethyl acetate (10:1 in volume ratio). By distilling away the solvent from the pale yellow eluate under a reduced pressure, 3.7 g. of the faint yellow powder of 7-phenylacetamidodesacetoxycephalosporanic acid 1-pivaloyloxyethyl ester was obtained. The nuclear magnetic resonance spectra of the product coincided completely with the structure.

Elementary analysis as $C_{23}H_{28}N_2O_6S$:

	C(%)	H(%)	N(%)	S(%)
Calculated:	59.98	6.13	6.08	6.96
Found:	59.85	6.27	6.01	6.73.

Example 87B.

In 15 ml. of dimethylformamide were suspended 3.0 g. of sodium 7-(2-thienylacetamido)cephalosporanate and 0.45 g. of potassium bicarbonate and then after adding to the suspension 2.0 g. of 1-acetoxypropyl bromide, the mixture was stirred for 16 hours at room temperature. The reaction mixture thus obtained was concentrated under a reduced pressure at a low temperature and the residue thus obtained was mixed with water. An oily material thus formed was extracted with dichloromethane. The extract was washed with aqueous sodium bicarbonate solution and then water, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure. The residue was subjected to a silica gel column chromatography and the product thus adsorbed was developed with a mixture of benzene and ethyl acetate (3:1 in volume ratio). The solvent was distilled away from the eluate under a reduced pressure to provide 1.8 g. of the yellowish crystalline powder of 7-(2-thienylacetamido)cephalosporanic acid 1-acetoxypropyl ester.

The infrared absorption spectra of the product coincided completely with the structure.

Elementary analysis as $C_{21}H_{24}N_2O_6S_2$:

Calculated: N 5.64%
Found: N 5.59%.

Example 88.

In 27 ml. of dichloromethane was dissolved 2.65 g. of 7-phenylacetamidodesacetoxycephalosporanic acid.1-pivaloyloxyethyl ester and after adding to the solution 2.4 ml. of N,N-dimethylaniline and then 1.33 g. of phosphorus pentachloride with stirring under cooling to −30°C., the mixture was stirred for two hours and 50 minutes at a temperature of −15°C. to −10°C. To the greenish reaction mixture thus prepared was added dropwise 18.5 ml. of absolute methanol at a temperature of lower than −20°C. and thereafter, the mixture was further stirred for 1 hour and 45 minutes at −20°C. Further more, 4 ml. of N,N-dimethylaniline and 1.43 g. of D(−)-α-phenylglycylchloride hydrochloride were added to the mixture with stirring at a temperature of lower than −20°C. and then the resultant mixture was allowed to stand overnight at a temperature of lower than −20°C. The reaction mixture thus formed was mixed with saturated sodium chloride solution and after shaking the mixture, the aqueous layer thus formed was separated from the dichloromethane layer formed. The aqueous layer thus separated was extracted with dichloromethane and the dichloromethane extract was combined with the dichloromethane layer recovered above and the mixture was dried over anhydrous magnesium sulfate and the the solvent was distilled away from the mixture under a reduced pressure. The residue was mixed with ether and the white precipitates thus formed were recovered by filtration. The precipitates were dissolved in water and the aqueous solution thus prepared was washed well with ethyl acetate, saturated with sodium chloride, and then extracted several times each with dichloromethane. The extracts were combined and the mixture was washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and the solvent was distilled away under a reduced pressure. By adding ether to the residue thus obtained, 1.95 g. of the white powder of 7-(α-aminophenylacetamido)desacetoxycephalosporanic acid 1-pivaloyloxyethyl ester hydrochloride having a melting point of 147°C. The infrared absorption spectra of the product and the NMR spectra of the product coincided completely with the structure.

Elementary analysis as $C_{23}H_{30}N_3O_6SCl$:

Calculated: N 8.21%
Found: N 8.02%.

Example 89.

In 20 ml. of dichloroethane was dissolved 1.6 g. of 7-(2-thienylacetamido)cephalosporanic acid 1-acetoxypropyl ester and after adding to the solution 1.36 ml. of N,N-dimethylaniline and then 0.75 g. of phosphorus pentachloride under cooling to −20°C., the mixture was stirred for 2 hours and 30 minutes at a temperature of −15°C. to −10°C. Then after cooling the faint brown solution thus obtained to −30°C., 13.5 ml. of absolute methanol was added thereto and the mixture was stirred for one hour and 30 minutes at −20°C. Furthermore, 2.26 ml. of N,N-dimethylaniline and 0.85 g. of D(−)-α-phenylglycylchloride hydrochloride were added to the mixture at −20°C., and the resultant mixture was stirred for one hour at −20°C.

To the reaction mixture thus prepared was added 15 ml. of saturated aqueous sodium chloride solution followed by shaking, the dichloroethane layer was recovered. The dichloroethane layer thus obtained was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under a reduced pressure. The residue thus formed was mixed with ether and the white precipitates thus formed were recovered by filtration. The precipitates were dissolved in about 40 ml. of water and the solution was washed thrice each with ethyl acetate and saturated with sodium chloride. Then, the oily material formed was extracted with dichloromethane. The extract was dried over anhydrous magnesium sulfate and concentrated. By adding ether to the residue, 0.95 g. of the white crystalline powder of 7-(α-aminophenylacetamido)cephalosporanic acid 1-acetoxypropyl ester hydrochloride having a melting point of 85—90°C. was obtained. The infrared absorption spectra and the NMR spectra of the product coincided completely with the structure.

Elementary analysis as $C_{23}H_{28}N_3O_8SCl$:

Calculated: N 7.75%
Found: N 7.62%.

Example 90.

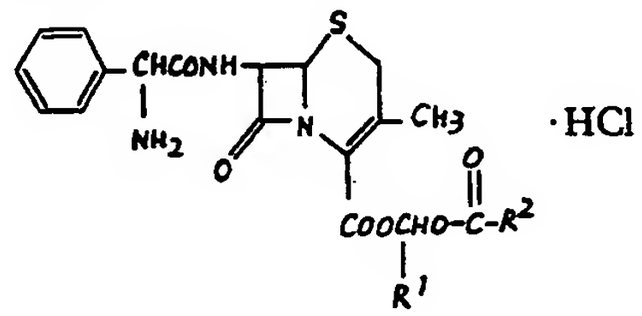
In 40 ml. of dichloroethane was dissolved 4.4 g. of 7-phenylacetamidodesacetoxycephalosporanic acid.1-propionyloxyethyl ester and after adding 4.2 ml. of dimethylaniline and then 2.3 g. of phosphorus pentachloride to the solution under cooling to a temperature of lower than −15°C., the mixture was stirred for 2 hours and 30 minutes at −10°C. After cooling the dark brown reaction mixture to −30°C., 30 ml. of absolute methanol was added dropwise to the reaction mixture and then the mixture was further stirred for one hour. Furthermore, 7.0 ml. of dimethylaniline and 2.5 g. of D(−)-α-phenylglycylchloride.hydrochloride were added to the mixture in four steps at −20°C. After stirring further the mixture for one hour, aqueous sodium chloride solution was added thereto and the resultant mixture was stirred well. Then, the organic layer thus formed was recovered and washed twice with saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under a reduced pressure. The residue thus obtained was mixed with 150 ml. of water and 50 ml. of ether followed by stirring. Then, the aqueous layer formed was recovered and washed with ether and then ethyl acetate. Then, by adding sodium chloride to the aqueous layer to practice salting out, a faint green oily material was formed, which was extracted with dichloromethane. The extract was dried over anhydrous magnesium sulfate and concentrated. When absolute ether was added to the residue thus obtained, 3.7 g. of the white powder of 7-(α-aminophenylacetamido)desacetoxycephalosporanic acid 1-propionyloxyethyl ester hydrochloride was obtained.

$[\alpha]_D^{18} = +74.4$ (C=1, methanol)

Elementary analysis as $C_{21}H_{26}N_3O_6SCl$:

Calculated: N 8.68%
Found: N 8.65%.

By following the similar procedure to Examples 86—90, the compounds of the following formula were prepared.



TABLE

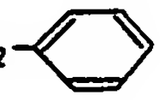
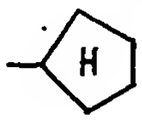
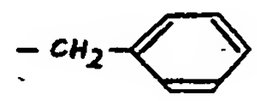
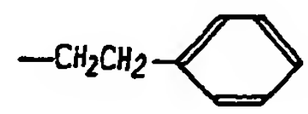
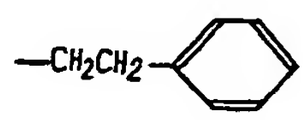
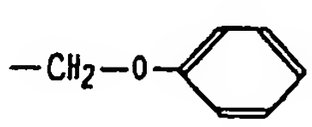
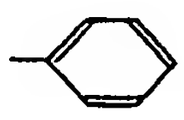
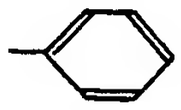
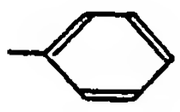
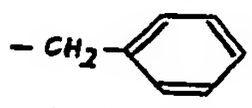
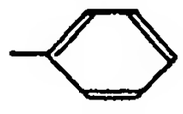
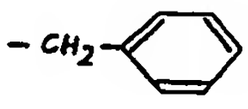
Example Number	R^2	R^1	$[\alpha]_D^{18}$ (c=1, chloroform)	Yield (%)	Elcmentary analysis Calculated N(%)	Found N(%)
91		$-CH_2CH_3$	+53.1	77	7.50	7.44
92	$-CH_2CH_3$	$-CH_2CH_3$	+57.4	69	8.44	8.26
93	$-CH_2CH_3$	$-CH_2CH_2CH_3$	+49.2	73	8.21	8.23
94		$-CH_2CH_2CH_3$	+52.2	81	7.42	7.33
95	$-CH_3$	$-CH_2CH_2CH_3$	+55.7	75	8.44	8.23
96	$-(CH_2)_6CH_3$	$-CH_2CH_2CH_3$	+76.6	44	7.22	7.12
97	$-CH(CH_2CH_3)_2$	$-CH_2CH_2CH_3$	+62.3	66	7.58	7.39
98	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$	+54.1	78	7.99	8.08

TABLE (Continued)

Example Number	R^2	R^1	$[\alpha]_D^{18}$ (c = 1, chloroform)	Yield (%)	Elementary analysis Calculated N(%)	Found N(%)
99		$-CH_2CH_2CH_3$	+ 50.8	75	7.32	7.21
100	$-CH_2CH(CH_3)_2$	$-CH_2CH_2CH_3$	–	64	7.78	7.76
101	$-(CH_2)_3CH_3$	$-CH_2CH_2CH_3$	–	72	7.78	7.72
102	$-C(CH_3)_3$	$-CH_2CH_2CH_3$	+ 51.2	75	7.78	7.71
103	$-CH(CH_3)_2$	$-CH_2CH_2CH_3$	+ 50.0	71	7.99	7.82
104	$-C(CH_3)_3$	$-CH(CH_3)_2$	+ 52.6	80	7.78	7.65
105	$-CH_2CH_3$	$-CH(CH_3)_2$	+ 60.5	74	8.21	8.14
106	$-CH_3$		+ 48.3	68	7.50	7.36
107	$-CH_2CH_3$		+ 48.2	72	7.32	7.25
108	$-CH_2CH_3$	$-CCl_3$	+ 56.4	64	7.15	7.02
109	$-CH_2CH_2CH_3$		+ 45.5	35	7.12	6.83
110		$-CH_2CH_2CH_3$	+ 38.7	59	7.50	7.36
111	$-CH_2CH_3$		+ 46.6	44	7.70	7.53
112	$-CH_2CH_2CH_3$		+ 47.4	54	7.50	7.54
113			+ 47.1	59	6.91	6.83
114		$-(CH_2)_5CH_3$	+ 46.9	59	6.82	6.85
115	$-CH_2CH_3$	$-(CH_2)_5CH_3$	+ 54.9	51	7.58	7.45

Example 115A.

In 50 ml. of dimethylformamide was suspended 8.63 g. of 6-aminopenicillanic acid and then 8.3 ml. of triethylamine was added to the suspension followed by stirring at a temperature of lower than 10°C. to dissolve the 6-aminopenicillanic acid therein. To the solution was added dropwise 15.0 g. of 1-acetoxypropyl bromide with stirring at 10°C. and thereafter the mixture was stirred for 2 hours at room temperature.

To the reaction mixture was added 100 ml. of ethyl acetate and triethylamine hydrochloride thus formed was filtered off. The filtrate was, then, washed twice each with 30 ml. of saturated aqueous sodium chloride solution and then washed further with 50 ml. of 5% aqueous sodium bicarbonate solution and then 50 ml. of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then the solvent was distilled away under a reduced pressure at a low temperature. The oily residue was washed with petroleum ether and dried under a reduced pressure to provide 9.3 g. of yellow oily 6-aminopenicillanic acid 1-acetoxypropyl ester with a yield of 73.7%.

Infrared absorption spectra:
νNH_2; 3350 cm.$^{-1}$ (amino group)
$\nu C=O$; 1780 cm.$^{-1}$ (β-lactam), 1750—1760 cm.$^{-1}$ (ester).

Example 115B.

In 50 ml. of dimethylformamide was suspended 8.63 g. of 6-aminopenicillanic acid and then 8.3 ml. of triethylamine was added to the suspension followed by stirring to dissolve therein the 6-aminopenicillanic acid. To the solution was added dropwise 24.0 g. of α-benzoyloxybenzyl bromide with stirring at 10°C., and thereafter, the mixture was stirred for 2 hours at room temperature. Then, by treating the mixture as in Example 5, 13.0 g. of the yellow powder of 6-aminopenicillanic acid α-benzoyloxybenzyl ester was obtained with a yield of 76.4%.

Infrared absorption spectra:
νNH_2; 3350 cm.$^{-1}$ (amino group)
$\nu C=O$; 1780 cm.$^{-1}$ (β-lactam), 1740—1750 cm.$^{-1}$ (ester).

Example 116.

In 30 ml. of dichloromethane was dissolved 3.2 g. of 6-aminopenicillanic acid 1-acetoxypropyl ester. To the solution 2.5 g. of D(−)-α-phenylglycylchloride hydrochloride and 20 ml. of dichloromethane containing 1.4 ml. of triethylamine were added alternately, whereby the solution was maintained to a pH of about 3.

Then, after the mixture was stirred for 2 hours at the same temperature, the reaction product liquid was washed twice each with 30 ml. of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure at low temperature to provide an oily residue. To the residue were added 50 ml. of cold water and 20 ml. of ethyl acetate followed by stirring to dissolve the residue therein and after removing gummy insoluble matters from the solution, the aqueous layer formed was recovered. Then, after washing the aqueous layer with 20 ml. of ethyl acetate, 30 ml. of ethyl acetate was added in layer thereto and was saturated with sodium chloride.

Then, the ethyl acetate layer thus formed was recovered and the aqueous layer thus separated was further extracted with 20 ml. of ethyl acetate. The ethyl acetate extract was combined with the ethyl acetate layer recovered above and the mixture was washed with 20 ml. of cold and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at low temperature. To the residue was added 50 ml. of ether and the crystal formed was recovered by filtration. By washing the crystal with a small amount of ether and drying it, 2.6 g. of the white powder of ampicillin 1-acetoxypropyl ester hydrochloride having a melting point of 107—110°C. (decomposed) was obtained with a yield of 52.9%.

Elementary analysis as $C_{21}H_{28}N_3O_6SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	51.90	5.81	8.65	7.30
Found:	51.48	6.24	8.37	7.05.

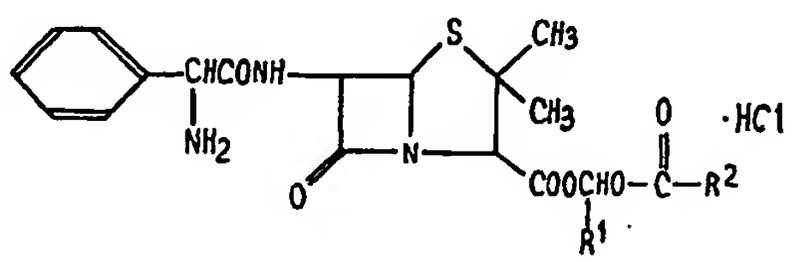
Example 117.

In 40 ml. of dichloromethane was dissolved 4.26 g. of 6-aminopenicillanic acid α-benzoyloxybenzyl ester and then 2.5 g. of D(−)-α-phenylglycylchloride hydrochloride and 20 ml. of dichloromethane containing 1.4 ml. of triethylamine were alternately and slowly added to the solution with stirring under cooling at a temperature of −5°C. to −10°C., whereby the reaction liquid was maintained at a pH of about 3. Thereafter, the mixture was stirred for 2 hours at the same temperature and the reaction mixture thus prepared was washed twice each with 30 ml. of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure at low temperature to provide an oily residue. To the residue were added 100 ml. of cold water and a mixture of 30 ml. of ethyl acetate and 20 ml. of petroleum benzine followed by stirring to dissolve therein the residue therein and after filtering away the gummy insoluble matters from the solution, the aqueous layer formed was recovered. The aqueous layer was washed with a mixture of 20 ml. of ethyl acetate and 10 ml. of petroleum benzine and then was mixed with a small amount of activated carbon followed by filtration. To the filtrate was added in layer 30 ml. of ethyl acetate and then sodium chloride was added thereto with stirring to saturate it. The ethyl acetate layer thus formed was recovered and the aqueous layer separated was further extracted twice each with 20 ml. of ethyl acetate. The ethyl acetate extracts were combined with the ethyl acetate layer recovered above and the mixture was washed with 30 ml. of cold and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure at low temperature. To the residue was added petroleum ether and the crystal thus formed was recovered by filtration, washed with a small amount of petroleum ether, and dried to provide 3.4 g. of the white powder of ampicillin α-benzoyloxybenzyl ester hydrochloride having a melting point of 145—146°C. (decomposed) with a yield of 57.1%.

Elementary analysis as $C_{30}H_{30}N_3O_6SCl$:

	C(%)	H(%)	N(%)	Cl(%)
Calculated:	60.45	5.07	7.05	5.95
Found:	60.16	5.60	6.89	6.20.

Furthermore, by following the similar procedures to Examples 116 and 117, the compounds having the following formula were prepared.



TABLE

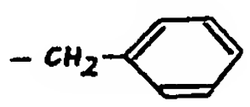
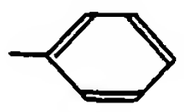
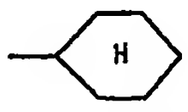
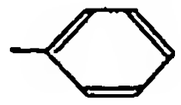
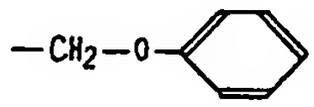
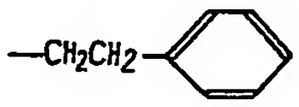
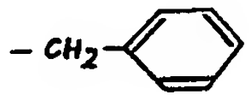
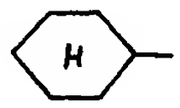
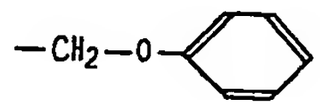
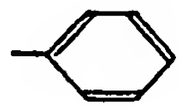
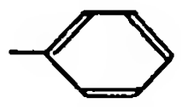
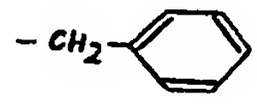
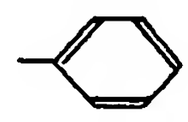
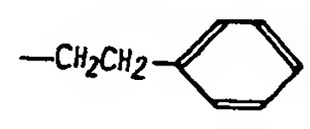
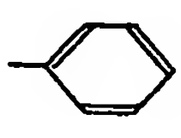
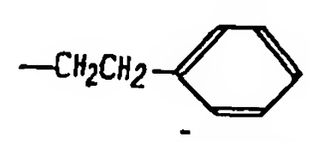
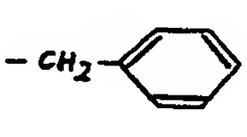
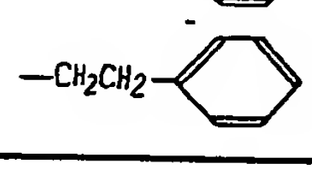
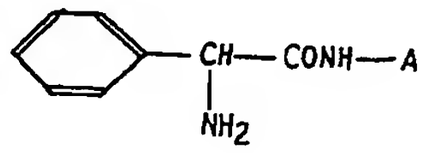
Example Number	R^2	R^1	Melting point (°C)
118	$-CH_3$	$-CH_3$	103 – 105
119	$-C(CH_3)_3$	$-CH_3$	111 – 114
120	$-CH_3$	$-CH=CH_2$	115 – 118
121		$-CH_2CH_2CH_3$	135 – 138
122	$-CH_2CH_2CH_2CH_3$		128 – 130
123		$-CH_3$	134 – 137
124		$-CH_3$	137 – 138
125		$-CH_3$	116 – 119
126	$-CH_3$		118 – 122
127	$-CH_3$	$-CCl_3$	148 – 149
128	$-CH_2CH_3$	$-CH_3$	107 – 110
129	$-(CH_2)_6CH_3$	$-CH_3$	104 – 108
130	$-CH(C_2H_5)_2$	$-CH_3$	88 – 107
131		$-CH_3$	150 – 152
132	$-CH_2CH_3$	$-CH_2CH_3$	100 – 104
133	$-(CH_2)_2CH_3$	$-CH_2CH_3$	113 – 120
134	$-CH(CH_3)_2$	$-CH_2CH_3$	130 – 136
135	$-C(CH_3)_3$	$-CH_2CH_3$	125 – 128
136	$-CH(CH_2CH_3)_2$	$-CH_2CH_3$	105 – 108
137	$-CH_3$	$-(CH_2)_2CH_3$	95 – 99
138	$-CH_2CH_3$	$-(CH_2)_2CH_3$	122 – 126
139	$-(CH_2)_2CH_3$	$-(CH_2)_2CH_3$	122 – 123
140	$-CH(CH_3)_2$	$-(CH_2)_2CH_3$	106 – 110
141	$-(CH_2)_6CH_3$	$-(CH_2)_2CH_3$	105 – 110
142	$-C(CH_3)_3$	$-(CH_2)_2CH_3$	111 – 115

TABLE (Continued)

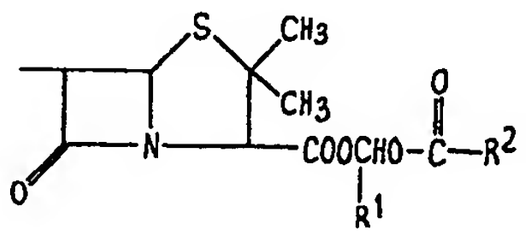
Example Number	R^2	R^1	Melting point (°C)
143	$-CH(CH_2CH_3)_2$	$-(CH_2)_2CH_3$	85 – 104
144		$-(CH_2)_2CH_3$	127 – 130
145		$-(CH_2)_2CH_3$	117 – 120
146	$-CH_3$	$-CH(CH_3)_2$	115 – 119
147	$-CH_2CH_3$	$-CH(CH_3)_2$	126 – 128
148	$-CH(CH_3)_2$	$-CH(CH_3)_2$	124 – 126
149	$-C(CH_3)_3$	$-CH(CH_3)_2$	127 – 130
150	$-CH_3$	$-(CH_2)_5CH_3$	108 – 112
151	$-CH_3$		139 – 140
152	$-C(CH_3)_3$		143 – 144
153			128 – 130
154	$-C(CH_3)_3$		128 – 129.5
155			136 – 140
156			105 – 110

WHAT WE CLAIM IS:—

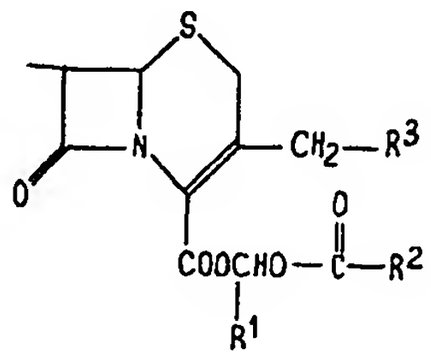
1. An acyloxyalkyl ester of 6-(α-aminophenylacetamido)penicillanic acid, 7-(α-aminophenylacetamido)cephalosporanic acid, or 7-(α-aminophenylacetamido)desacetoxycephalosporanic acid represented by the general formula



wherein A represents

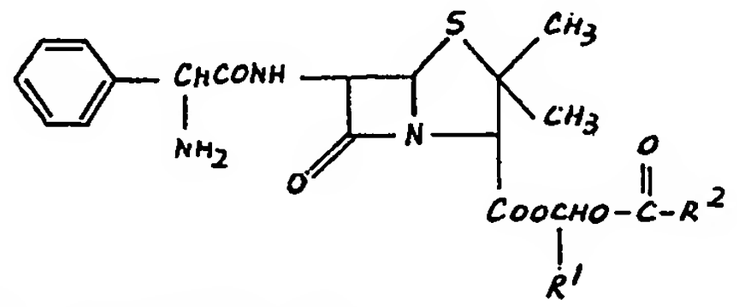


or



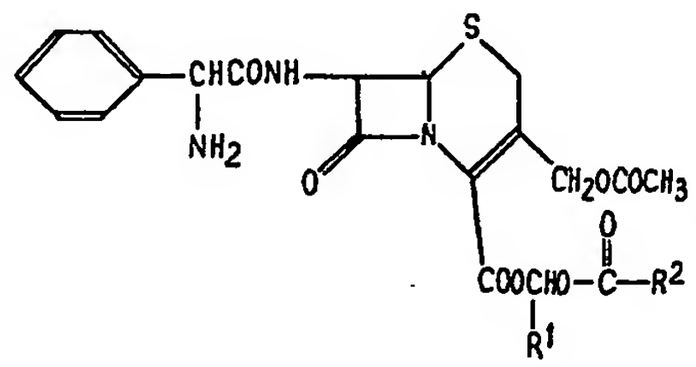
wherein R^1 and R^2 each represents an unsubstituted alkyl, cycloalkyl, alkenyl, or phenyl group or a substituted alkyl, cycloalkyl, alkenyl, or phenyl group wherein the substituent is a phenyl group, a phenoxy group, or a halogen atom or atoms and R^3 represents a hydrogen atom or an acetoxy group, and the mineral acid addition salts of said esters.

2. A hydrochloride of the 6-(α-aminophenylacetamido)penicillanic acid acyloxyalkyl ester represented by the general formula



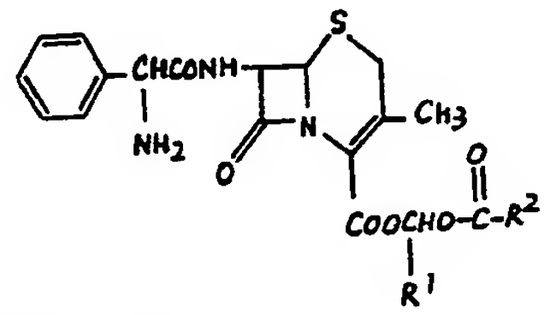
wherein R^1 and R^2 are as defined in claim 1.

3. A hydrochloride of the 7-(α-aminophenylacetamido)cephalosporanic acid acyloxyalkyl ester represented by the general formula



wherein R^1 and R^2 are as defined in claim 1.

4. A hydrochloride of the 7-(α-aminophenylacetamido)desacetoxycephalosporanic acid acyloxyalkyl ester represented by the general formula



wherein R^1 and R^2 are as defined in claim 1.

5. 6-(α-Aminophenylacetamido)penicillanic acid 1-acetoxypropyl ester hydrochloride.

6. 6-(α-Aminophenylacetamido)penicillanic acid 1-isobutyryloxybutyl ester hydrochloride.

7. 6-(α-Aminophenylacetamido)penicillanic acid 1-pivaloyloxybutyl ester hydrochloride.

8. 6-(α-Aminophenylacetamido)penicillanic acid α-butyryloxybenzyl ester hydrochloride.

9. 6-(α-Aminophenylacetamido)penicillanic acid α-benzoyloxybenzyl ester hydrochloride.

10. 6-(α-Aminophenylacetamido)penicillanic acid 1-acetoxy-3-phenylpropyl ester hydrochloride.

11. Cephalexin 1-acetoxyethyl ester hydrochloride.

12. Cephalexin 1-propionyloxybutyl ester hydrochloride.

13. Cephaloglycin 1-acetoxypropyl ester hydrochloride.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1974.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.